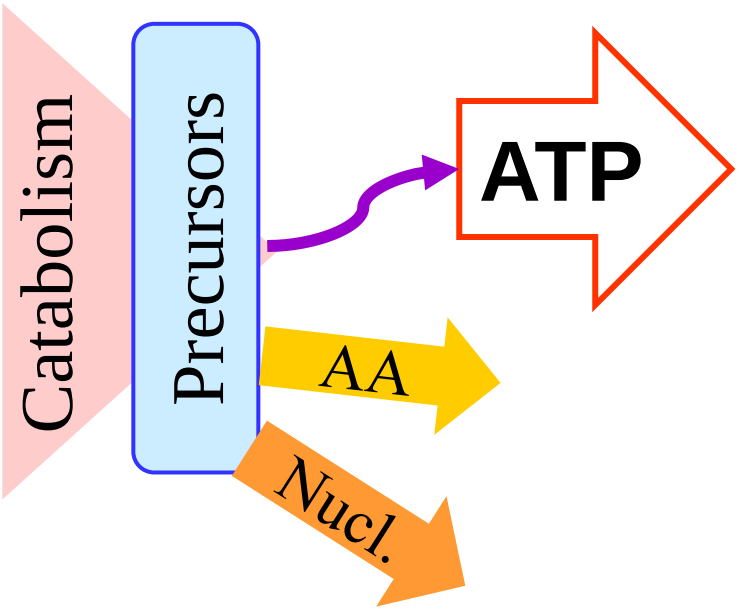
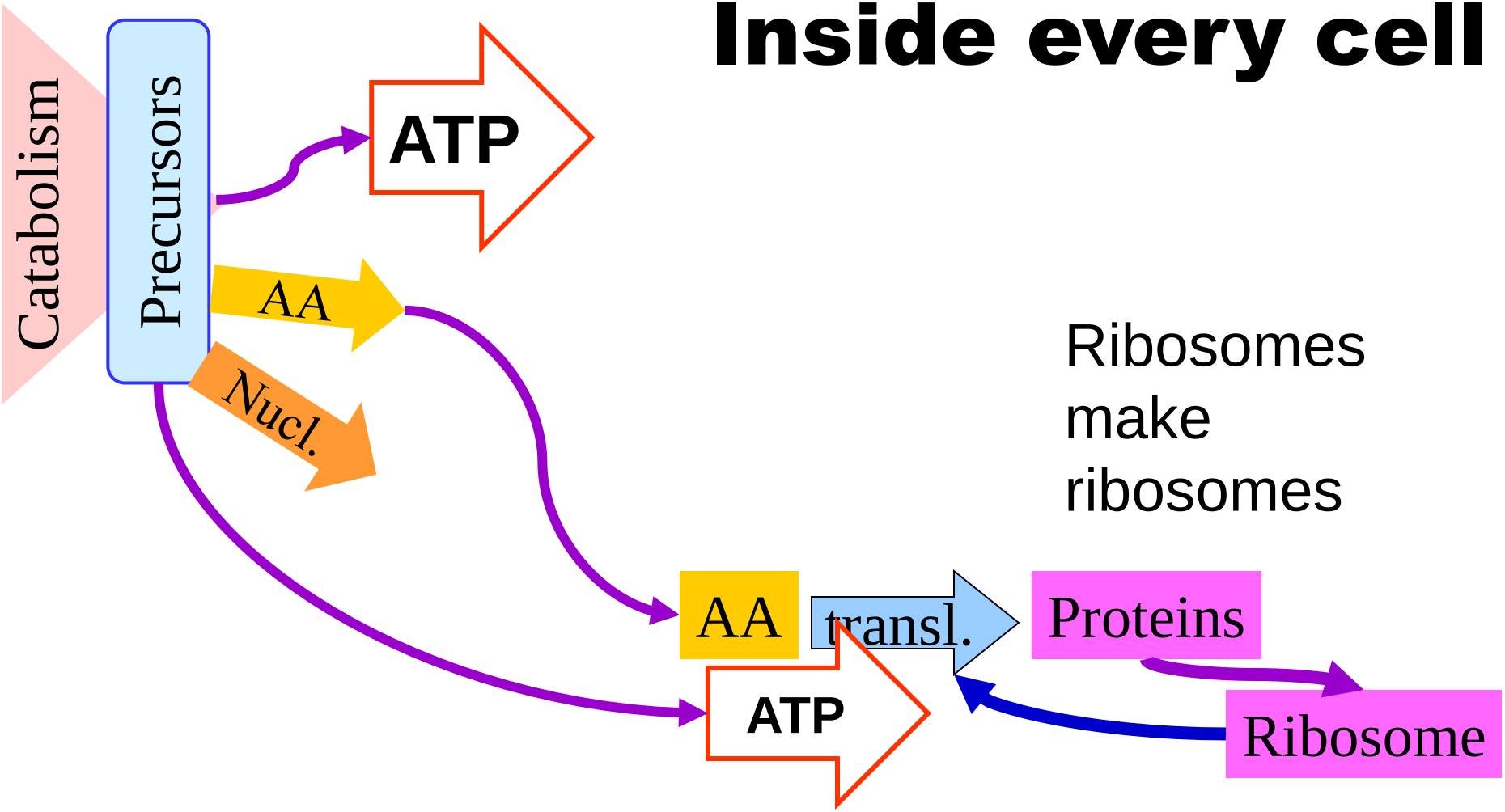
Inside every cell

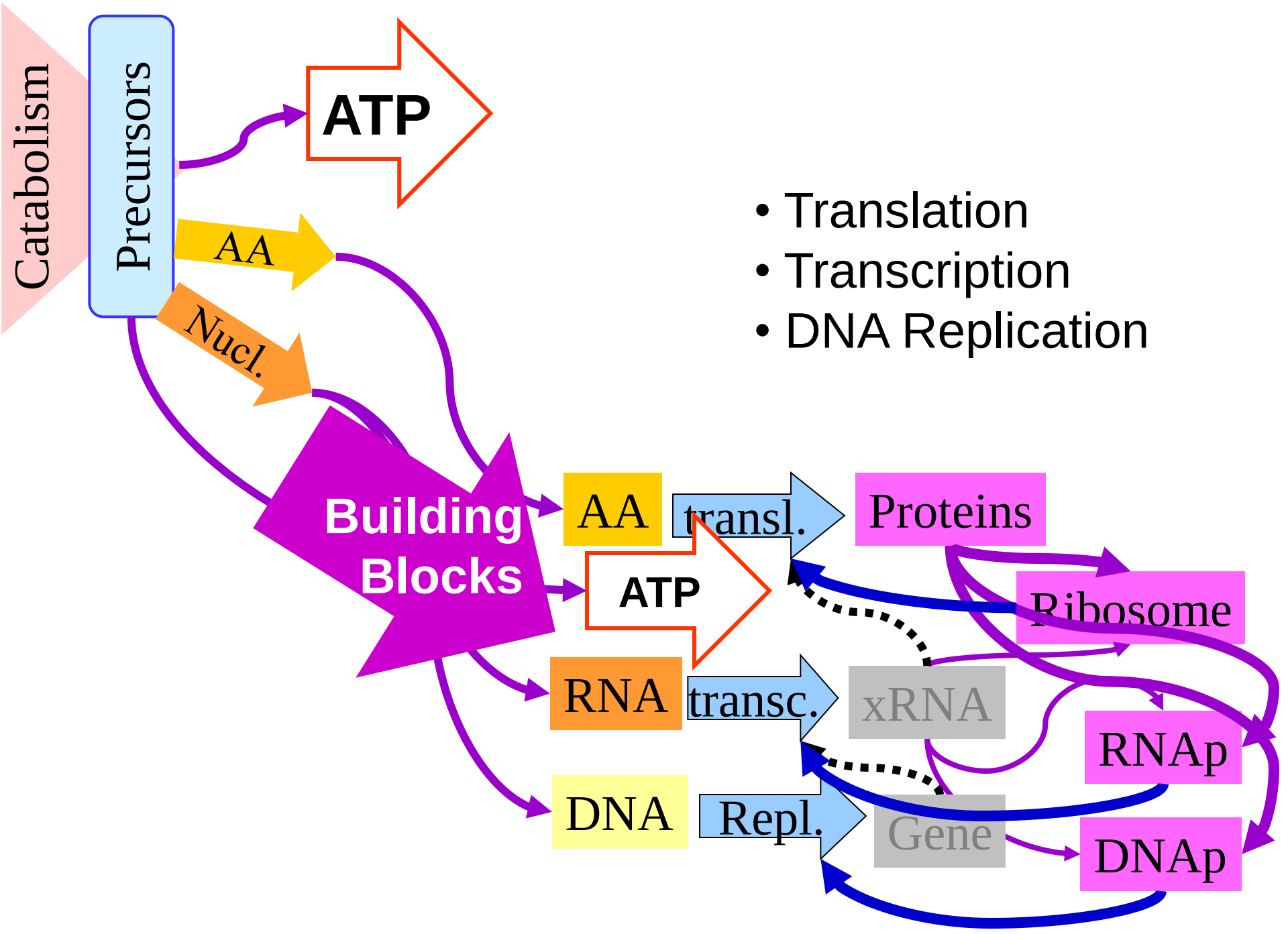


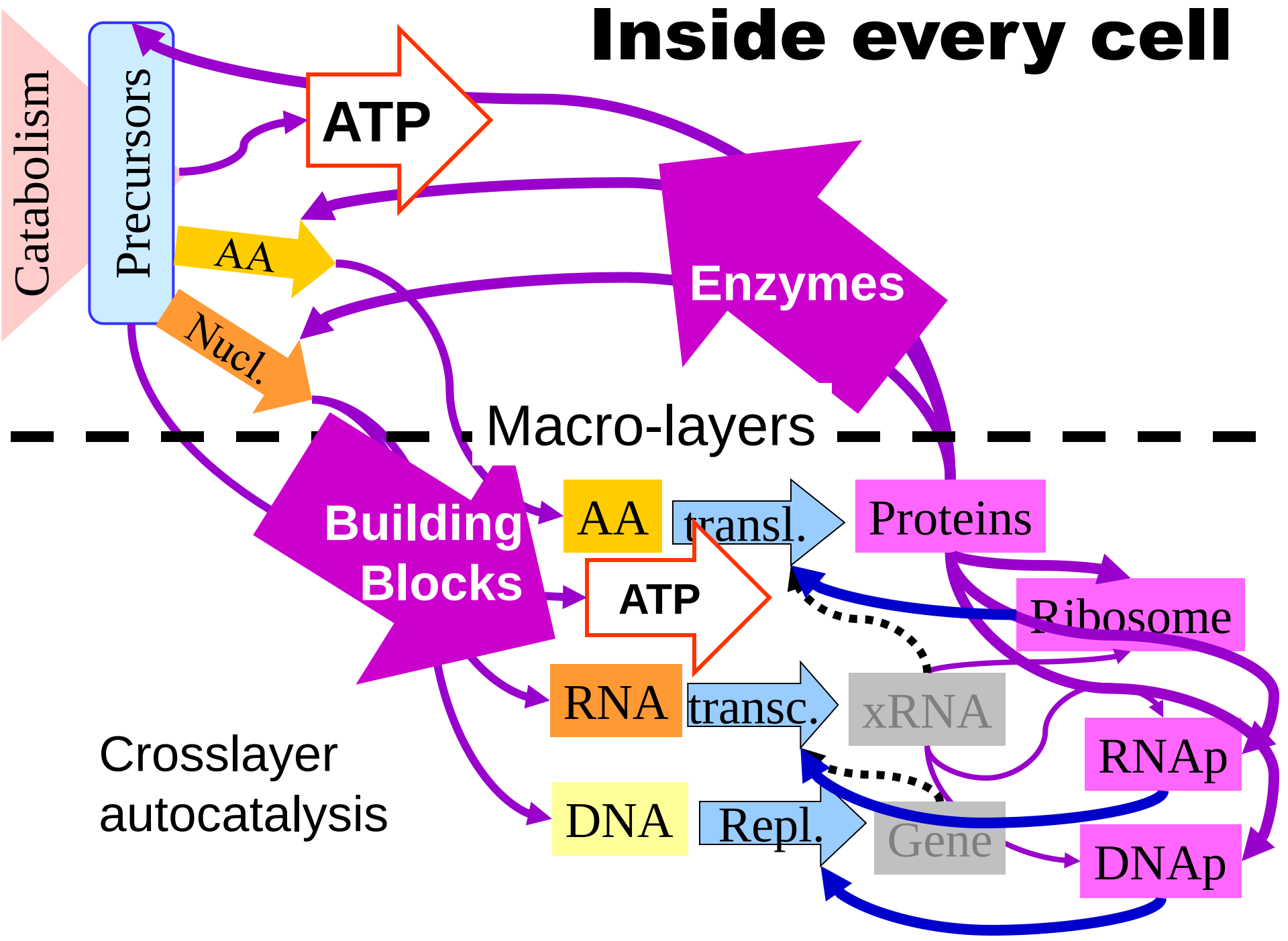
- **Autocatalytic feedback (essential)**
- Efficient processes
  - Minimal enzymes (lean manufacturing)
  - Long assembly process (simple steps)
- Limited control feedback

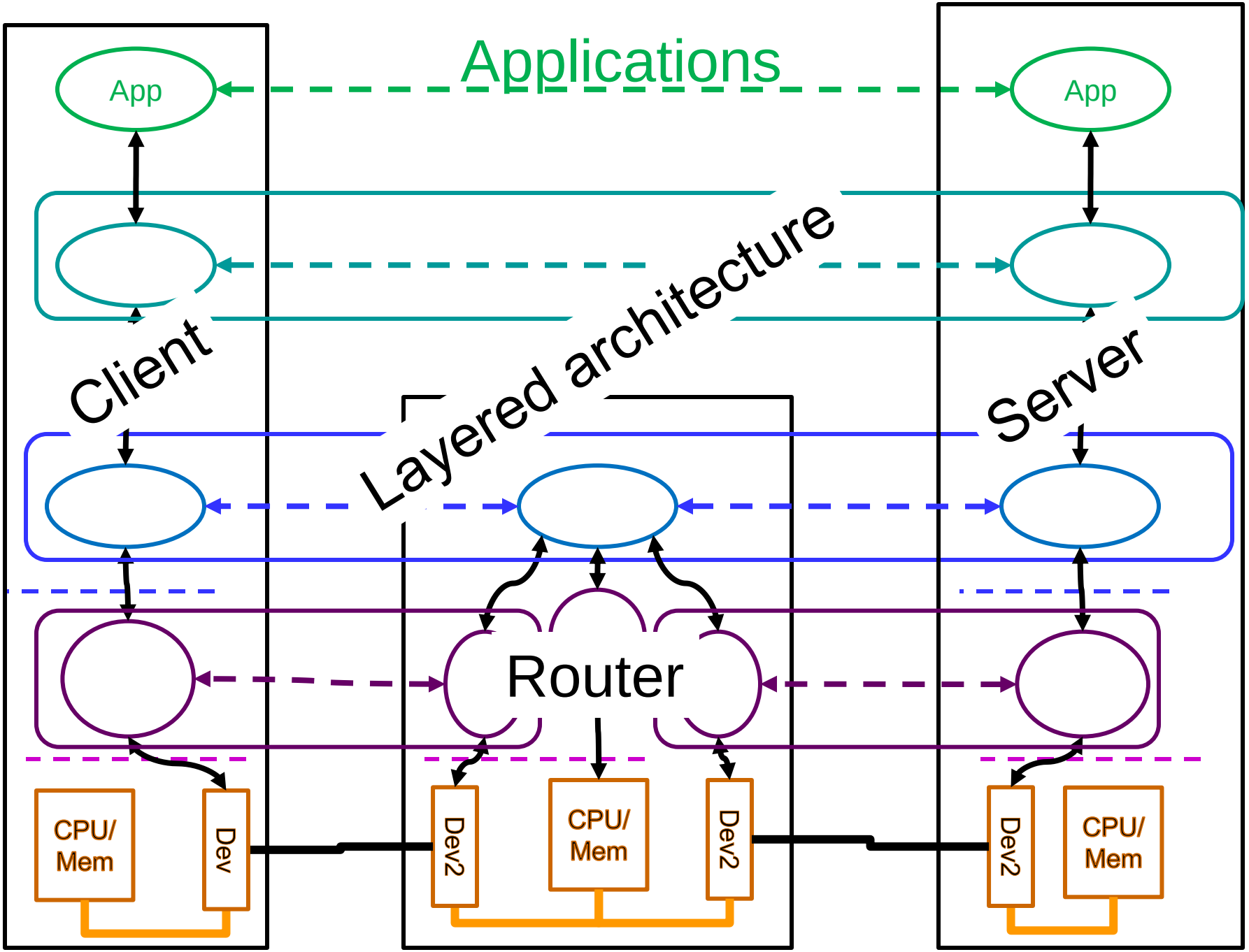
Inside every cell

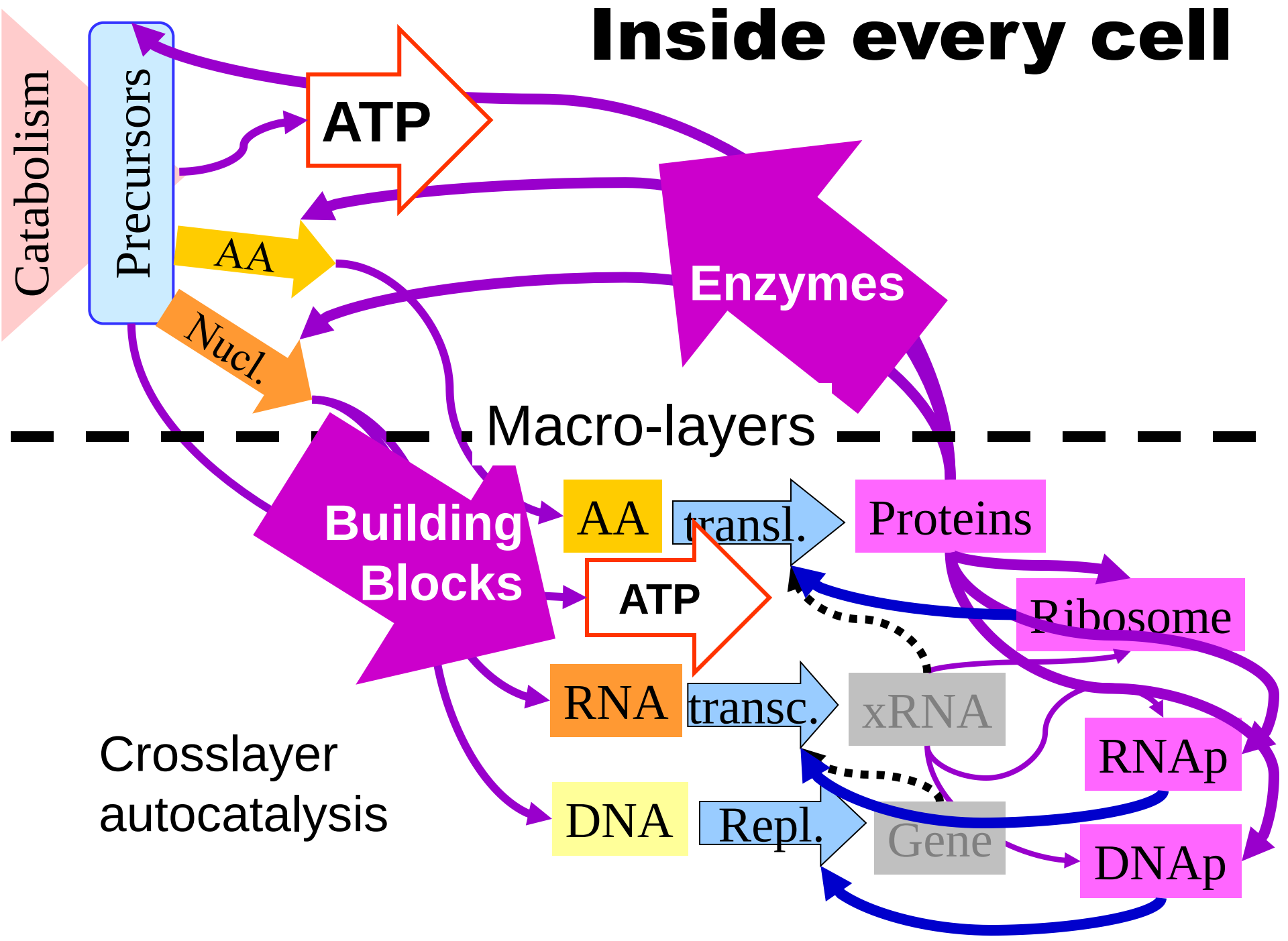


Translation: Amino acids polymerized into proteins


Catabolism
Precursors
ATP
AA
Nucl.
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
• Translation
• Transcription
• DNA Replication


Inside every cell
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Crosslayer autocatalysis


Applications
App
App
Client
Layered architecture
Server
Router
CPU/
Mem
Dev
Dev2
CPU/
Mem
Dev2
Dev2
CPU/
Mem


Inside every cell
Catabolism
Precursors
ATP
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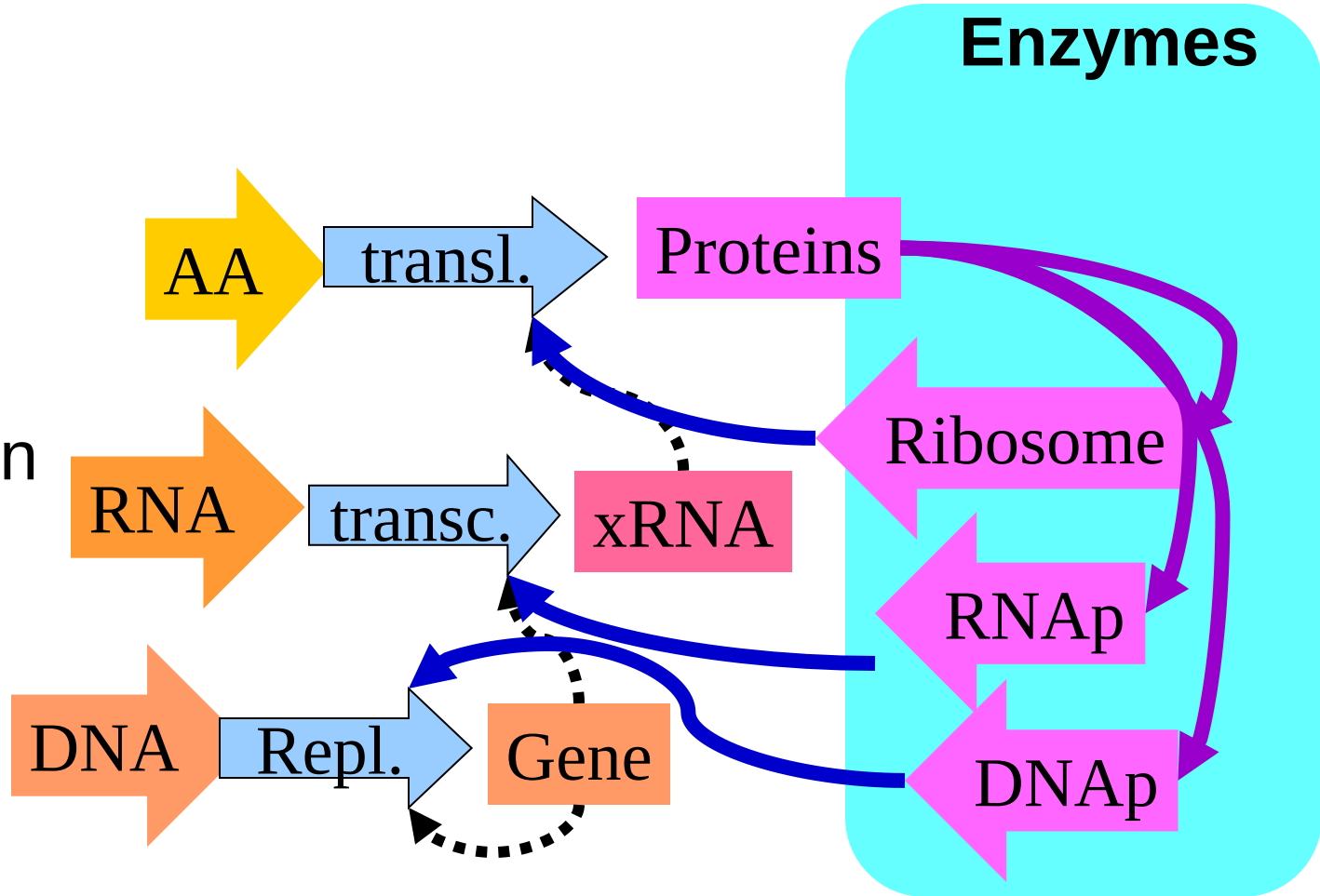
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Crosslayer autocatalysis

Lower layer autocatalysis
Macromolecules making …

Three lower layers? Yes:
- Translation
- Transcription
- Replication



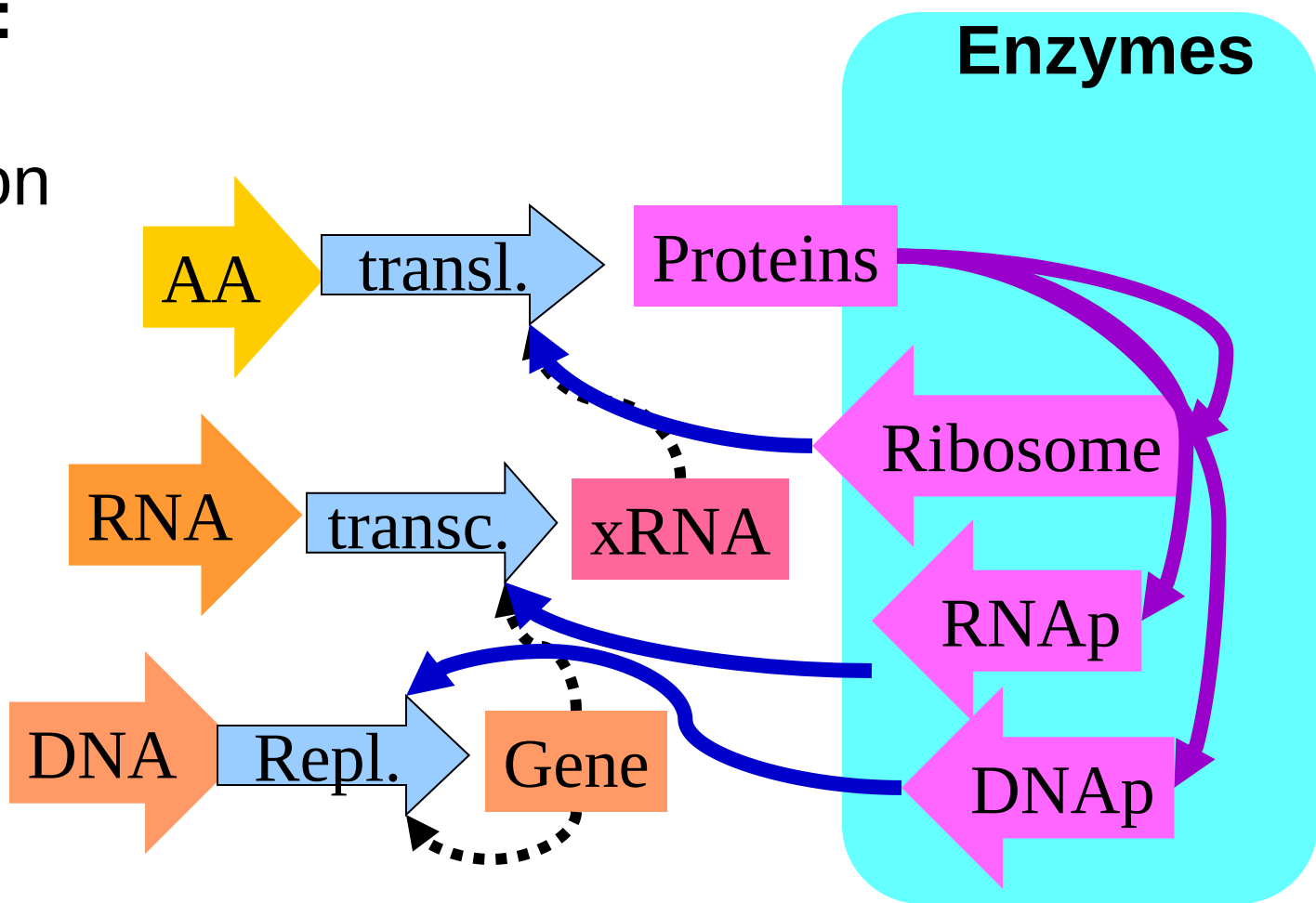
Autocatalytic within lower layers

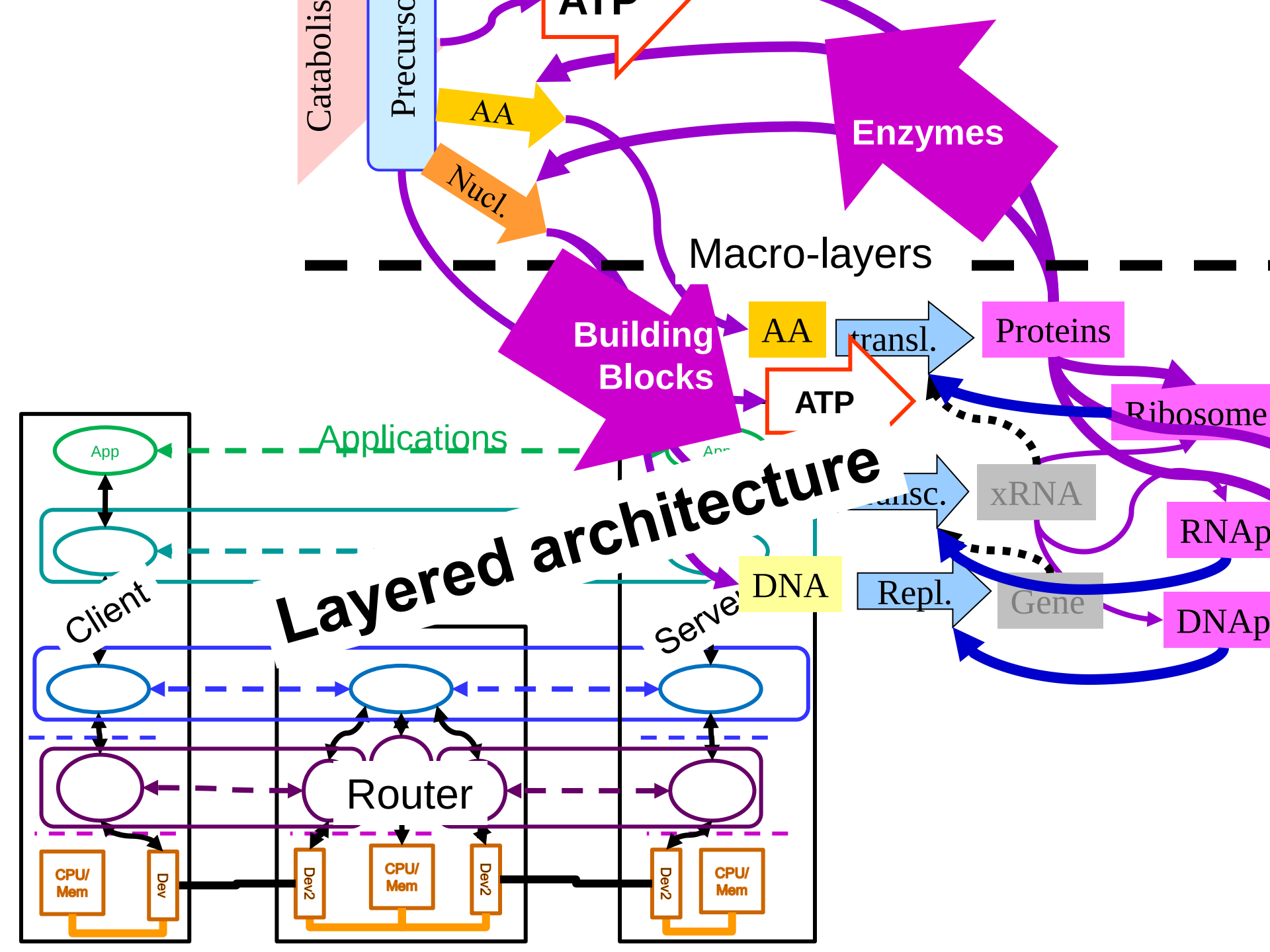
- Collectively self-replicating
- Ribosomes make ribosomes, etc

Three lower layers? Yes:

- Translation
- Transcription
- Replication

Naturally recursive



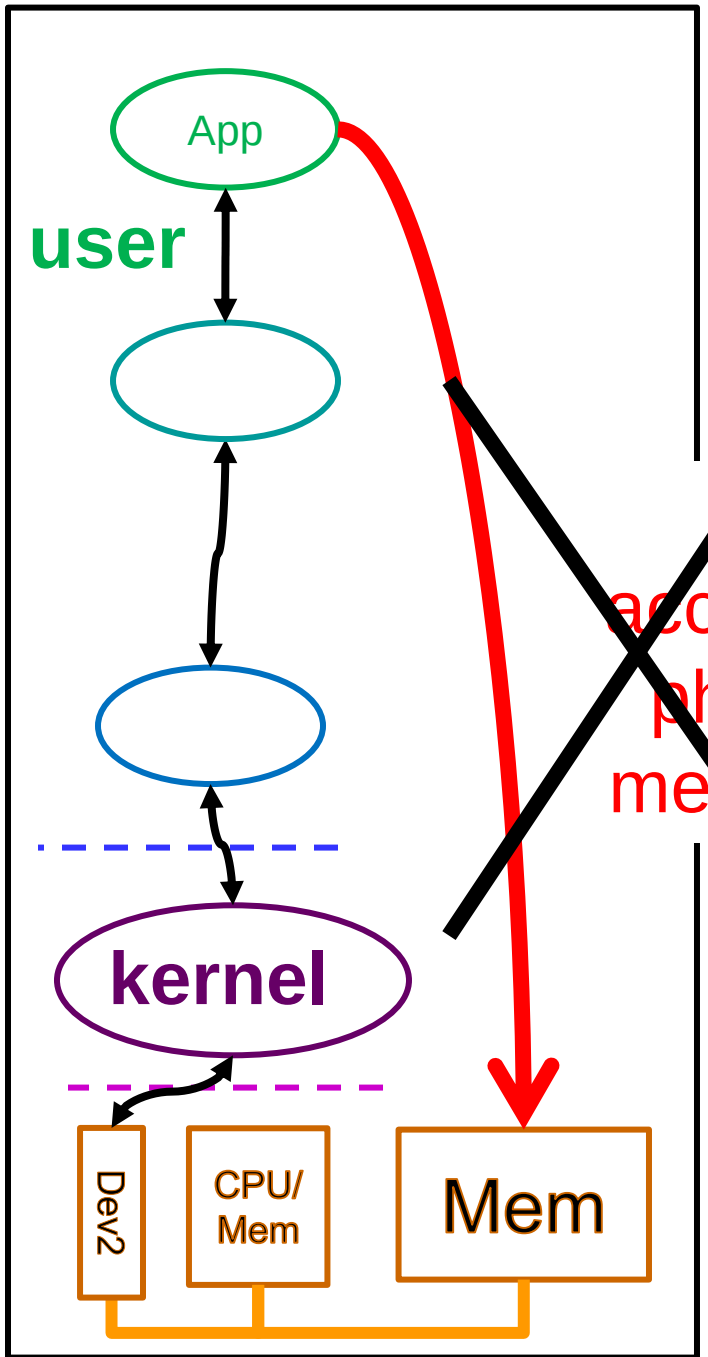

Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Macro-layers
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
Applications
xRNA
RNAp
DNA
Repl.
Gene
DNAp
Layered architecture
App
Client
Server
Router
CPU/ Mem
Dev
Dev2
CPU/ Mem
Dev2
Dev2
CPU/ Mem

Naming and addressing

- Names needed to locate objects
- 2.5 ways to resolve a name
  1. Exhaustive search, table lookup
  2. Name gives hints
- Extra ½ is for indirection
- Address is just a name that involves locations

Operating systems

- OS allocates and shares diverse resources among diverse applications
- Clearly separate (disaster otherwise)
  - Application name space
  - Logical (virtual) name/address space
  - Physical (name/) address space
- Name resolution within applications
- Name/address translation across layers



In operating systems:
Don't cross layers

Direct access to physical memory?

Benefits of stricter layering

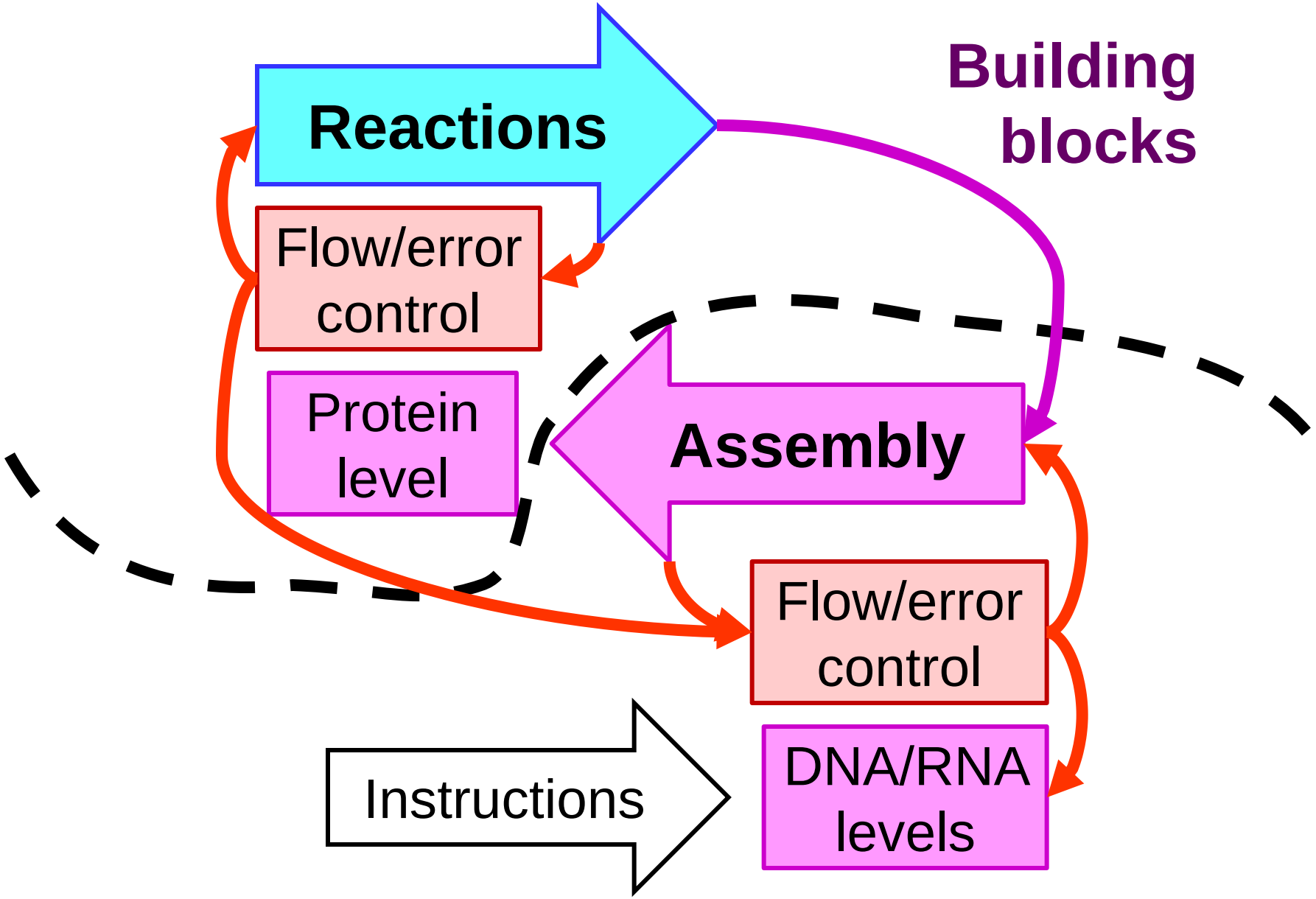
"Black box" effects of stricter layering

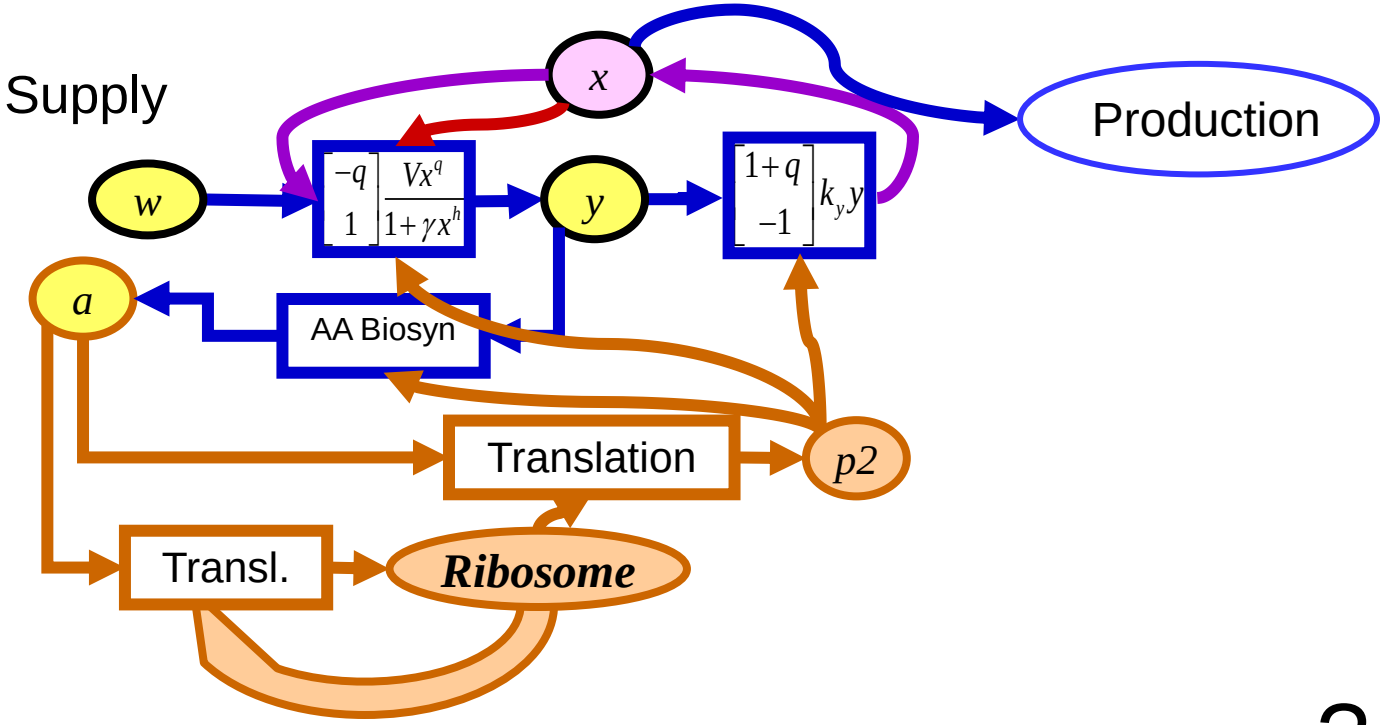
- Portability of applications
- Security of physical address space
- Robustness to application crashes
- Scalability of virtual/real addressing

- Optimization/control by duality?

Bacterial architecture

- More complex macro-layering of function
  - Upper: Metabolism, envelope, signaling, building blocks
  - Lower: Proteins & macromolecule synthesis, replication
- Cleaner layering of control
  - Transcription factors
  - 2 component signal transduction
- Name/address resolution
  - Global, exhaustive by fast diffusion within layers
  - Highly structured interactions between layers
- Limited scalability
  - Limited to small volumes
  - Control proteins scale super-linearly with enzyme numbers


Reactions
Building blocks
Flow/error control
Protein level
Assembly
Flow/error control
Instructions
DNA/RNA levels



? ?

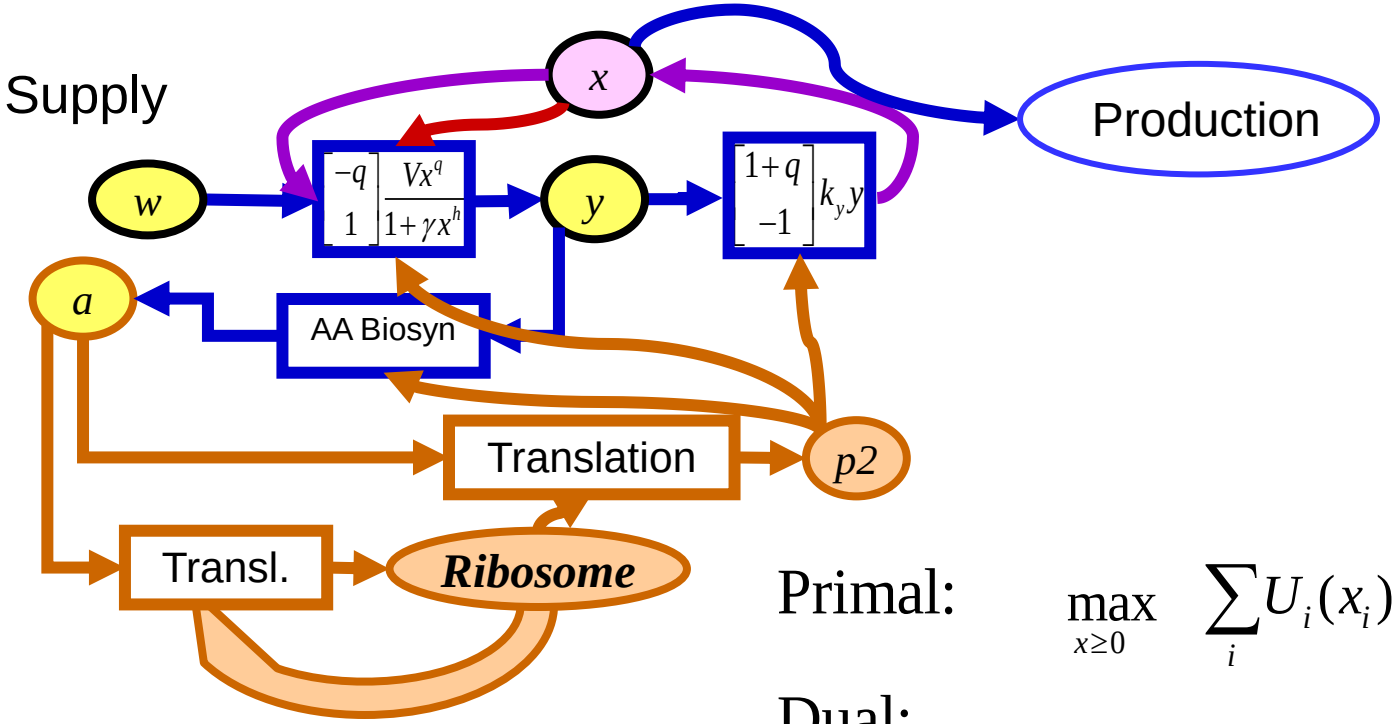
Does it fit the framework?
Yes, but it takes some explaining and no one has worked out the details.

$$\max_{x \geq 0} \quad \sum_i U_i(x_i) + \sum_l V_l(w_l)$$

$$\text{subj to} \quad R(G)\, x \leq c(w, \mathbf{P})$$

$$x \in C(\mathbf{P})$$

? ?



No duality gaps?
Multipath routing?
Coherent pricing?

Primal: $\max_{x \geq 0} \sum_i U_i(x_i)$ subject to $Rx \leq c$

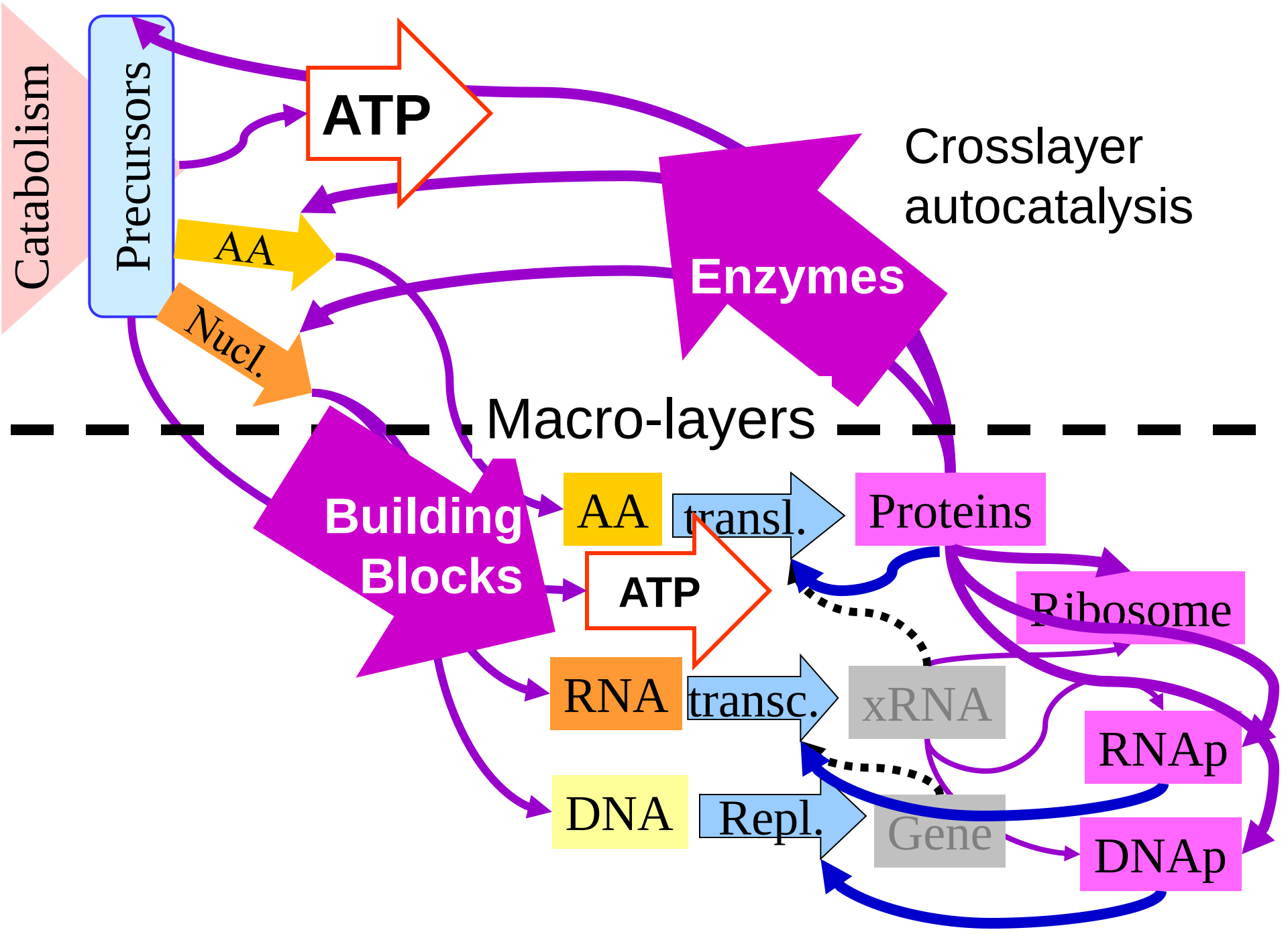
Dual:

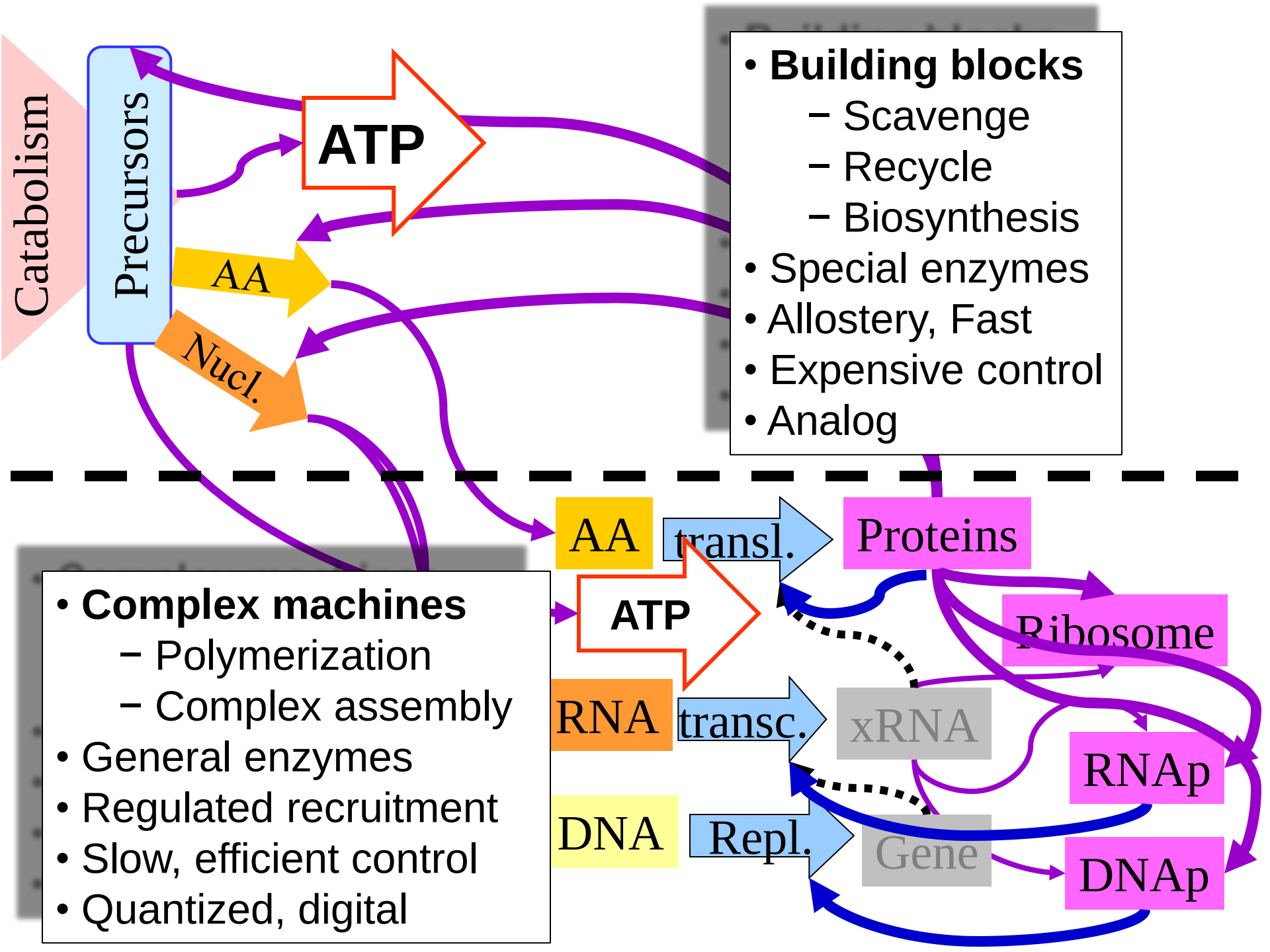
$$\min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - \sum_l p_l \left(R_{li} x_i - c_l \right) \right) \right)$$

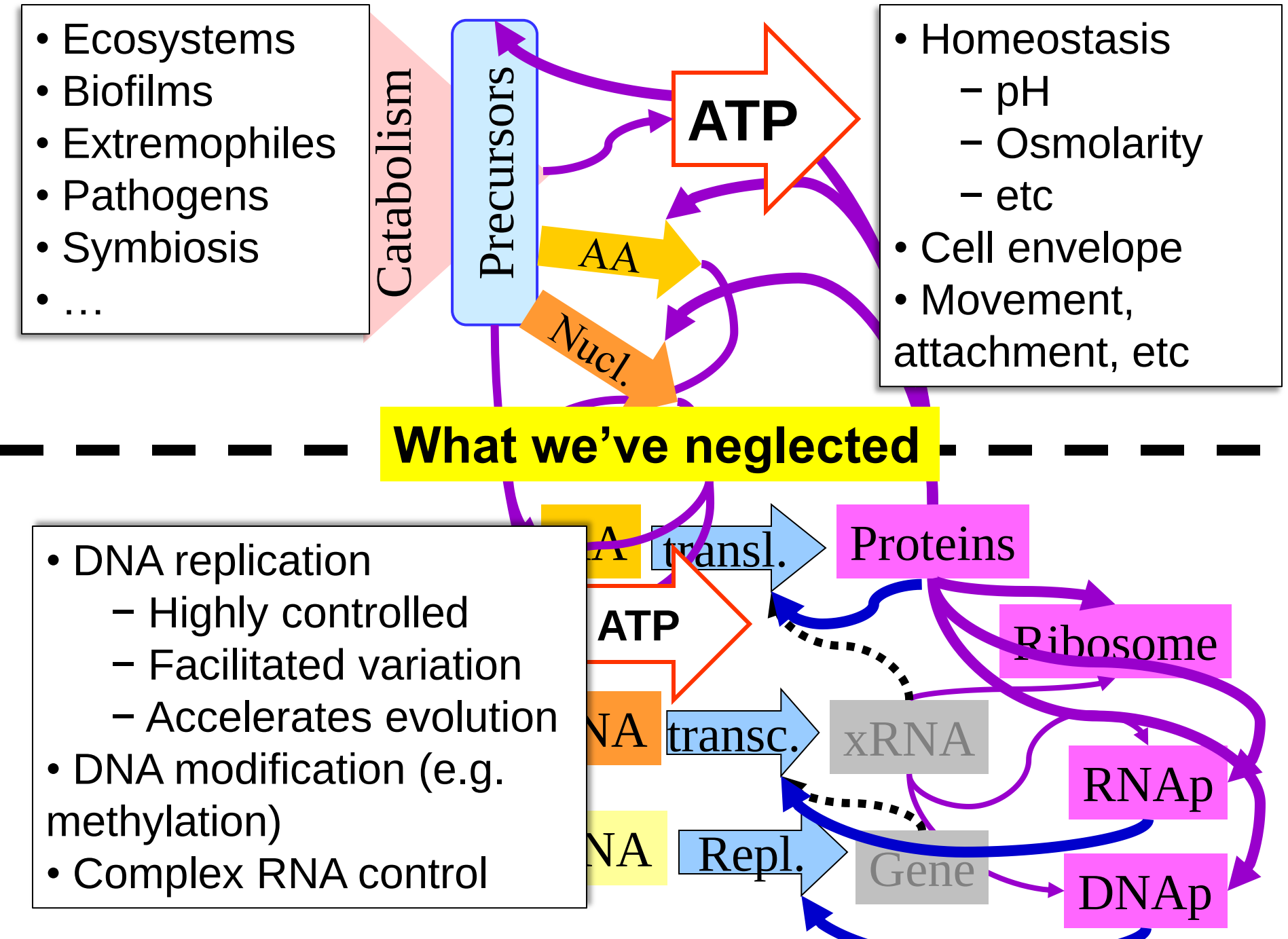
$$= \min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - x_i \sum_l R_{li} p_l \right) + \sum_l p_l c_l \right)$$

$$= \min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - x_i q_i \right) + \sum_l p_l c_l \right)$$

$$\Rightarrow U_i'(x_i) = q_i \Rightarrow x_i = \left(U_i' \right)^{-1} (q_i)$$

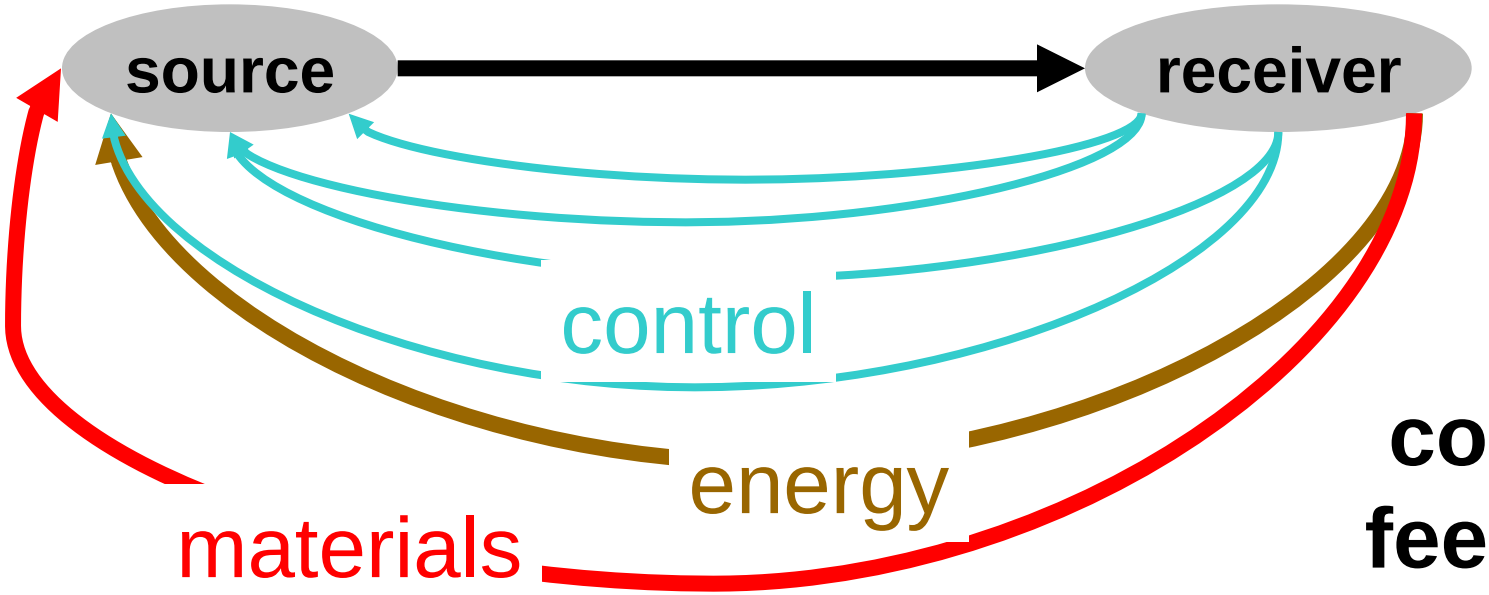

Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Crosslayer
autocatalysis
Macro-layers
Building
Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp


Catabolism
Precursors
ATP
AA
Nucl.
• Building blocks
– Scavenge
– Recycle
– Biosynthesis
• Special enzymes
• Allostery, Fast
• Expensive control
• Analog
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp
• Complex machines
– Polymerization
– Complex assembly
• General enzymes
• Regulated recruitment
• Slow, efficient control
• Quantized, digital

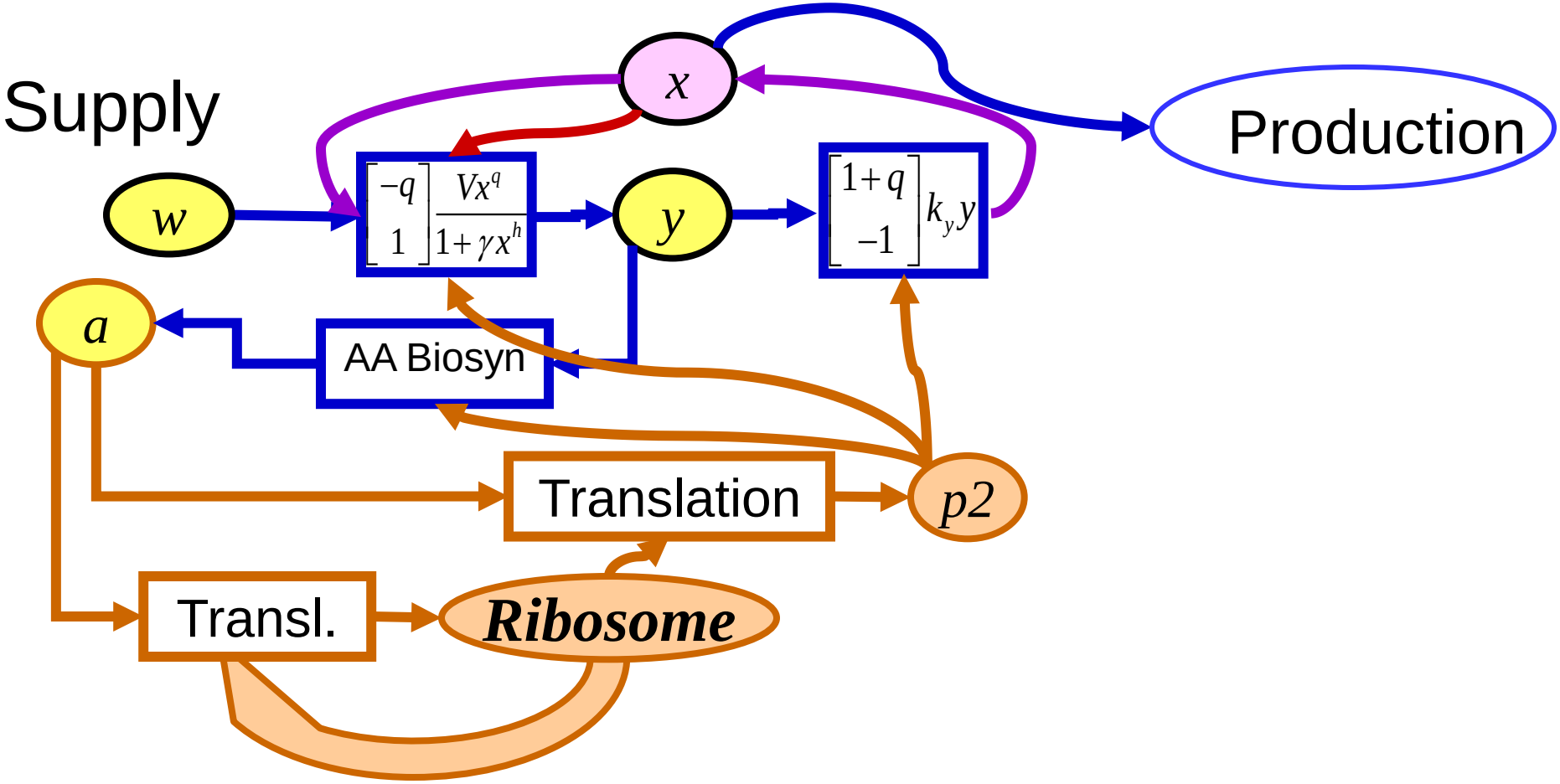

• Ecosystems
• Biofilms
• Extremophiles
• Pathogens
• Symbiosis
• …
Catabolism
Precursors
ATP
AA
Nucl.
• Homeostasis
– pH
– Osmolarity
– etc
• Cell envelope
• Movement, attachment, etc
What we've neglected
• DNA replication
– Highly controlled
– Facilitated variation
– Accelerates evolution
• DNA modification (e.g. methylation)
• Complex RNA control
transl.
Proteins
ATP
Ribosome
transc.
xRNA
RNAp
Repl.
Gene
DNAp

All these other feedbacks make feedback control harder, and in each layer biology appears to cleverly balance competing requirements.

$$\frac{1}{\pi}\int_0^{\infty} \ln\left|S(j\omega)\right| \frac{z}{z^2+\omega^2} d\omega \geq \ln\left|\frac{z+p}{z-p}\right|$$

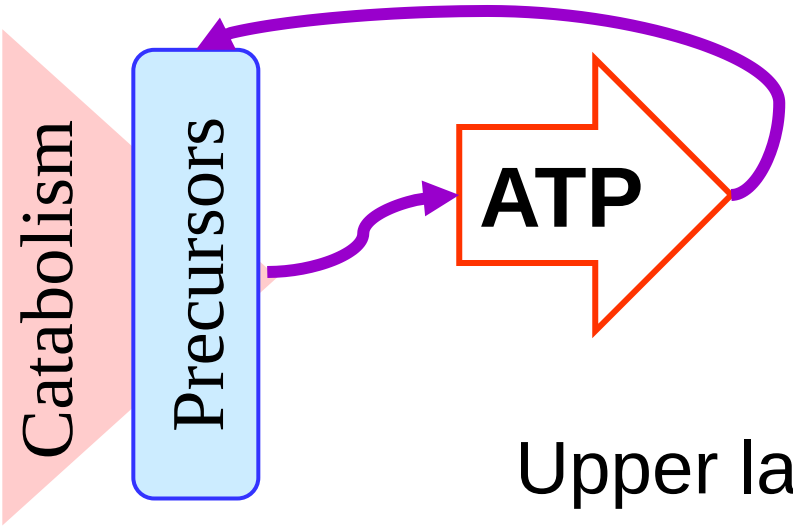


More complex feedback

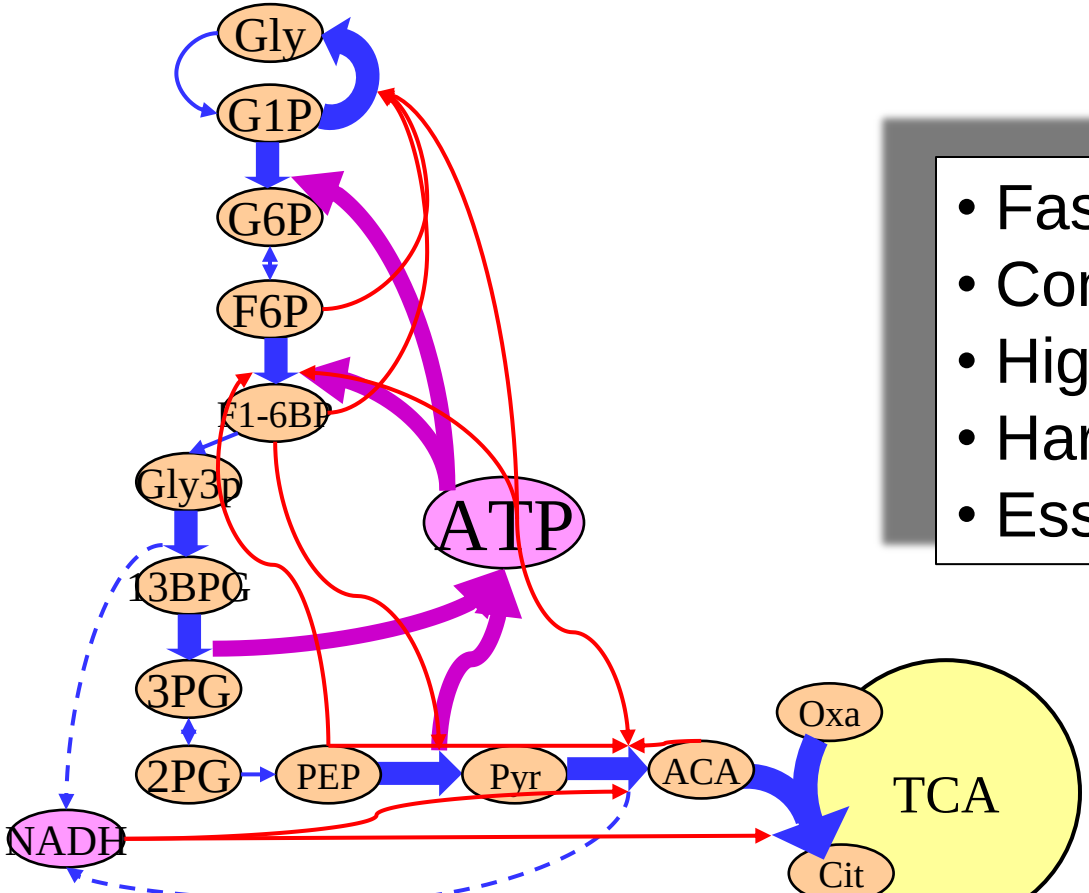


Main problem with autocatalytic networks

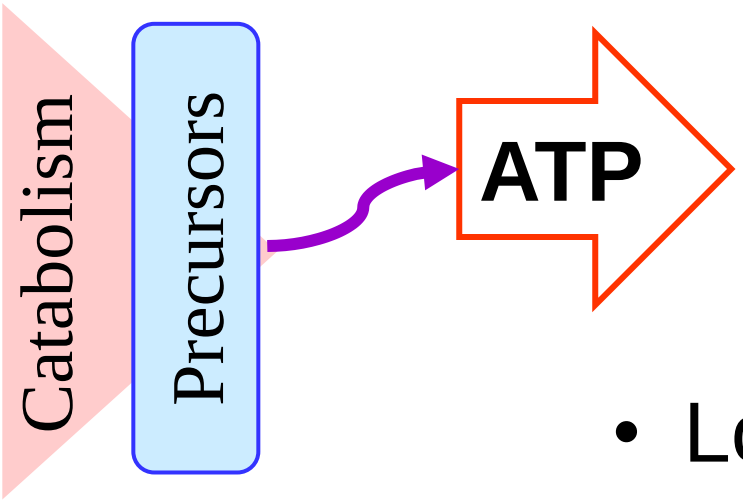
- Maximize production, but
- Balance risk to fluctuating supply
- (or control for fluctuating demand)



Upper layer autocatalysis

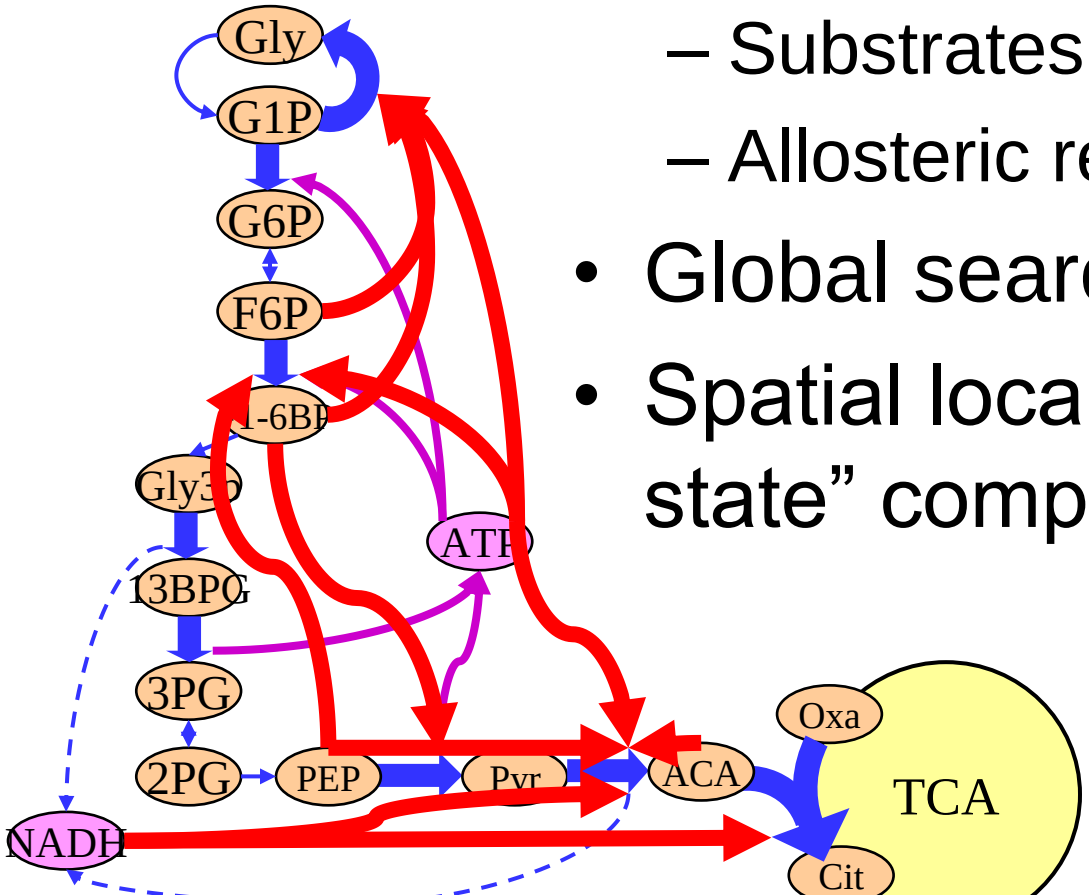


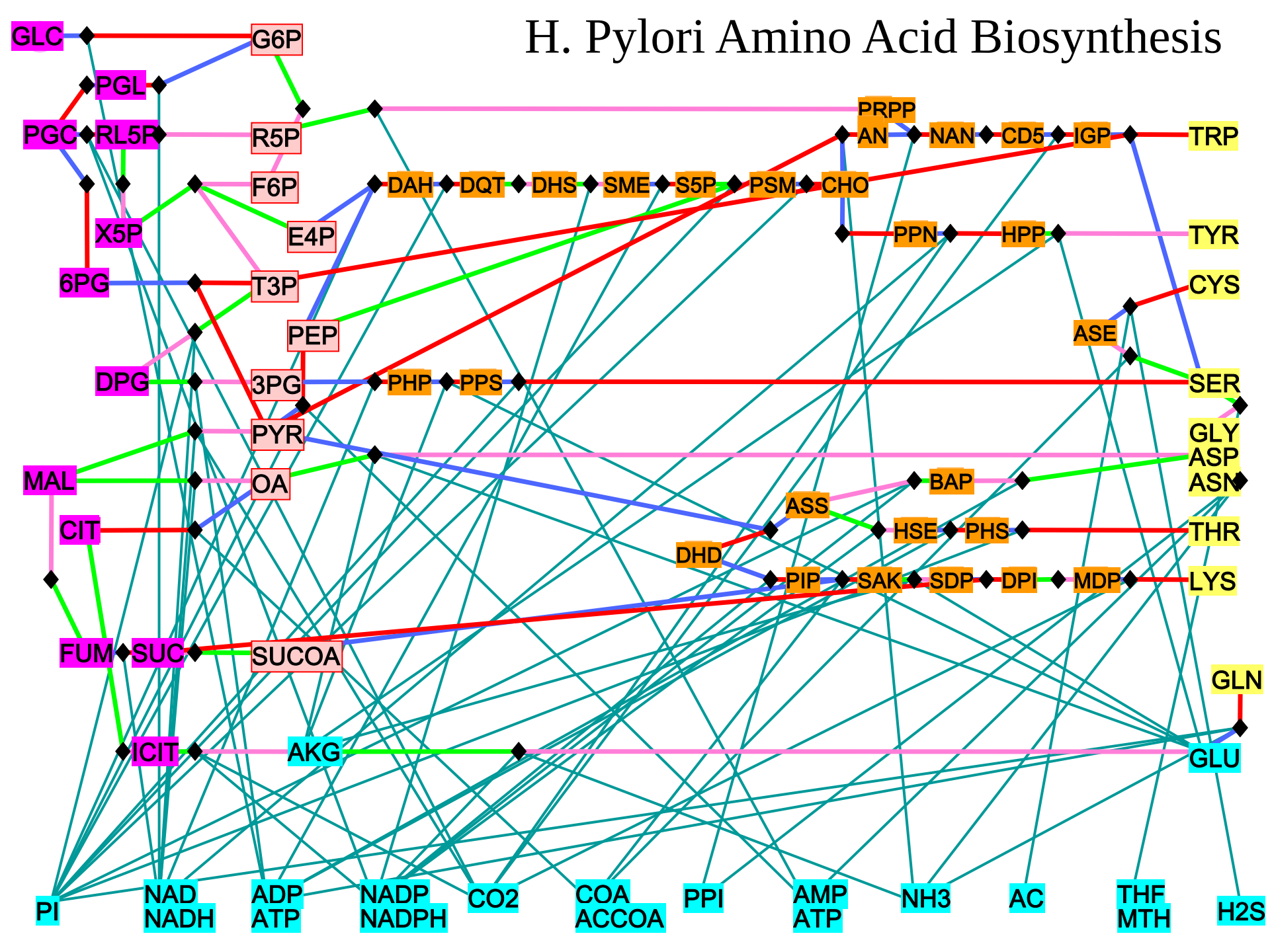
- Fastest allosteric control
- Complex proteins
- High metabolic overhead
- Hard to reprogram
- Essentially analog



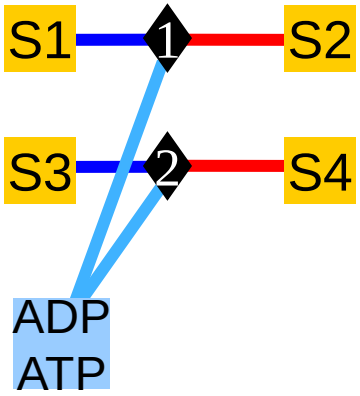
Name resolution?

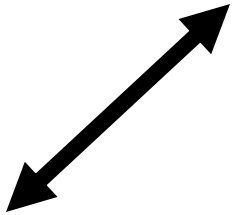
- Locating: Enzymes and
  - Substrates
  - Allosteric regulator
- Global search by diffusion
- Spatial localization by “solid state” complexes



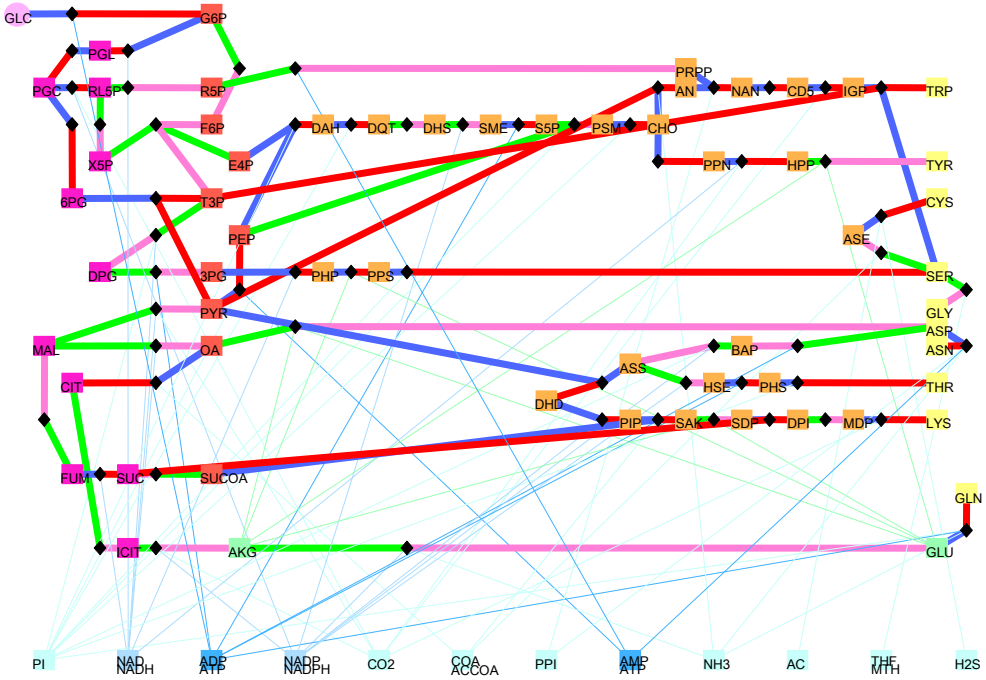

H. Pylori Amino Acid Biosynthesis
GLC
G6P
PGL
PGC
RL5P
R5P
F6P
X5P
E4P
6PG
T3P
PEP
DPG
3PG
PYR
MAL
OA
CIT
FUM
SUC
SUCOA
ICIT
AKG
PRPP
AN
NAN
CD5
IGP
TRP
DAH
DQT
DHS
SME
S5P
PSM
CHO
PPN
HPP
TYR
CYS
ASE
PHP
PPS
SER
GLY
ASP
ASN
BAP
ASS
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
GLN
GLU
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S

H Pylori amino acid biosynthesis

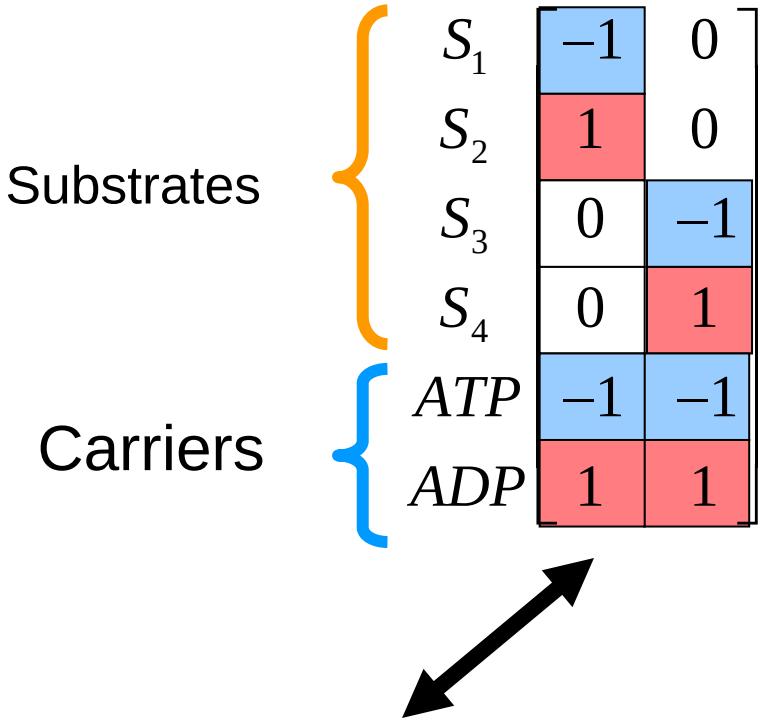




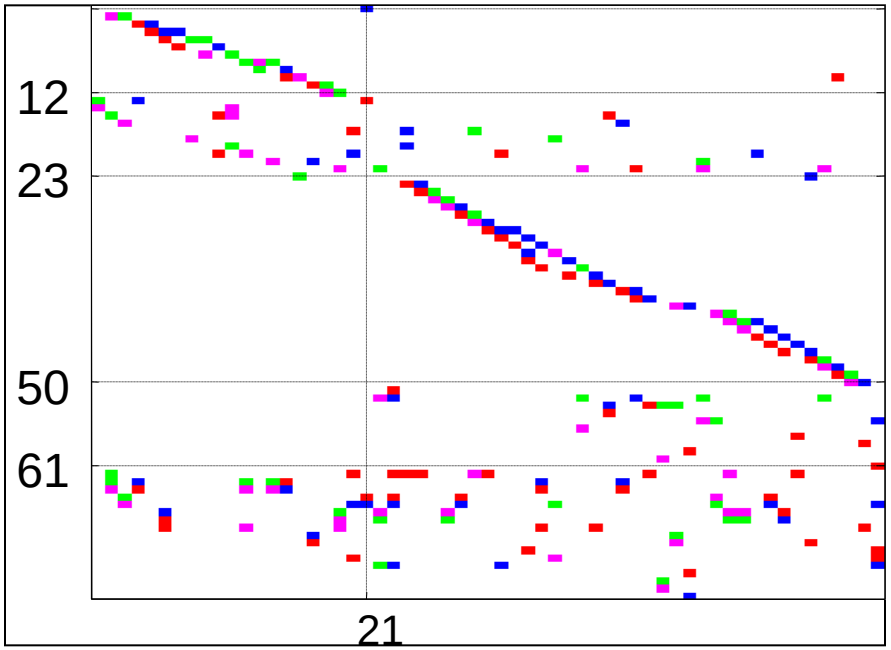
As a bipartite labeled graph.

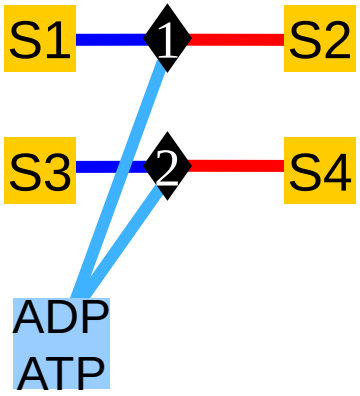


H Pylori amino acid biosynthesis



As a color coded (for reversibility) stoichiometry matrix.



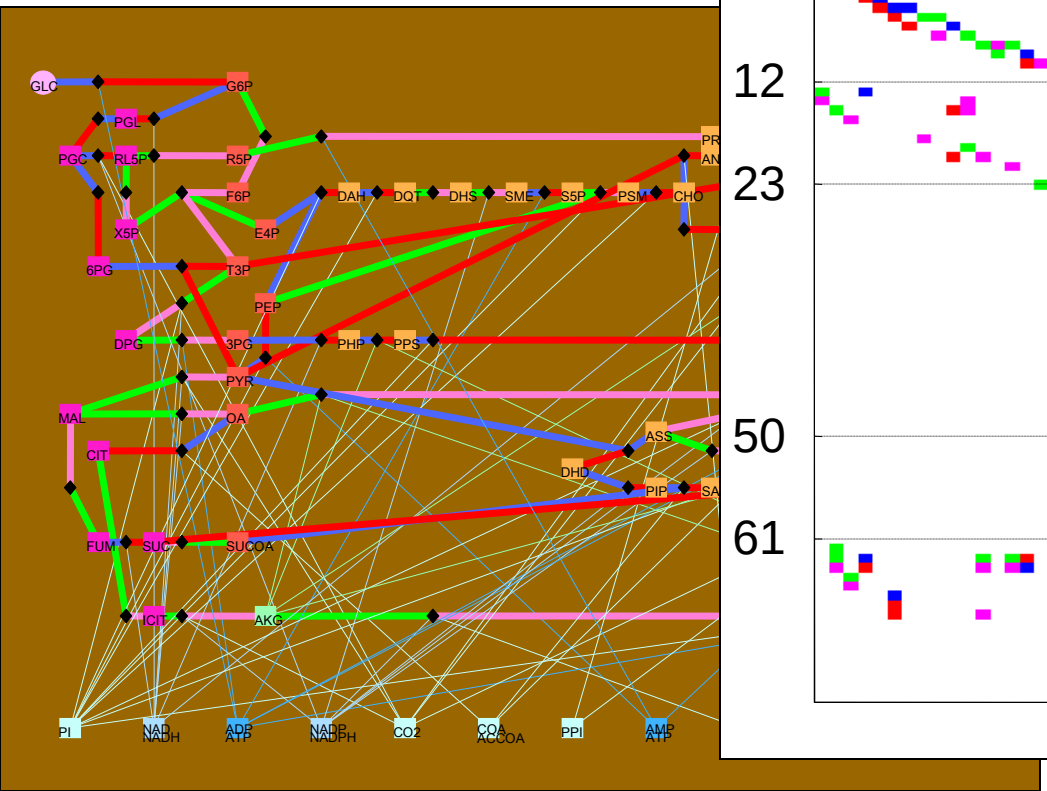


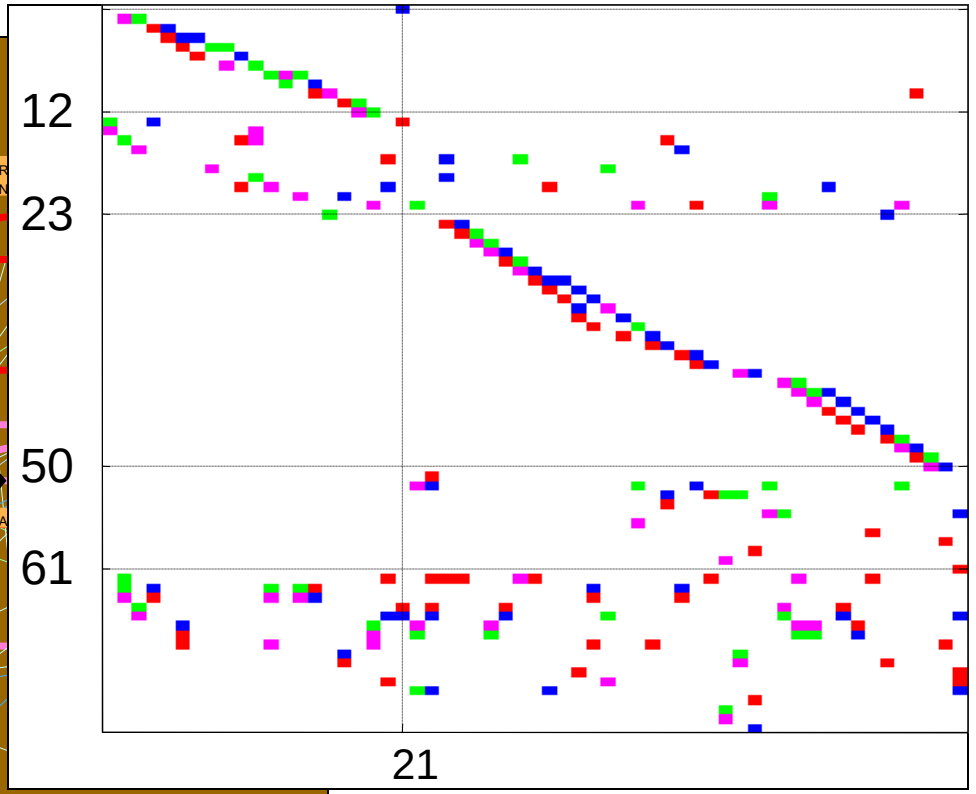
These are equivalent to each other but ***not*** to unipartite graphs.

Substrates

Carriers

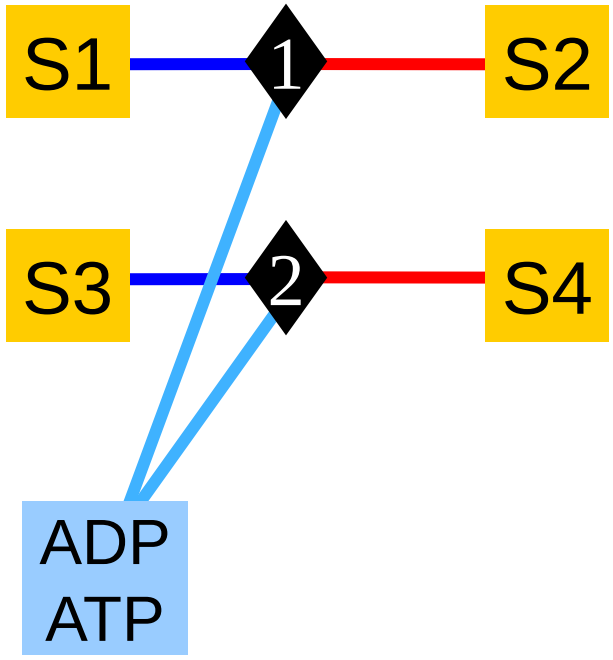
S_1	−1	0
S_2	1	0
S_3	0	−1
S_4	0	1
ATP	−1	−1
ADP	1	1



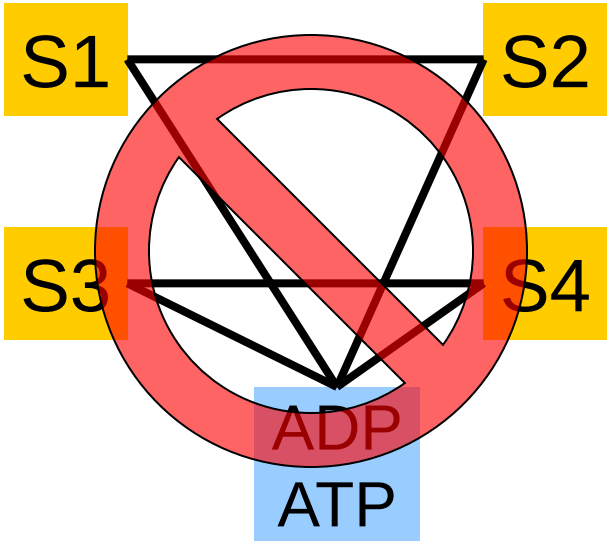


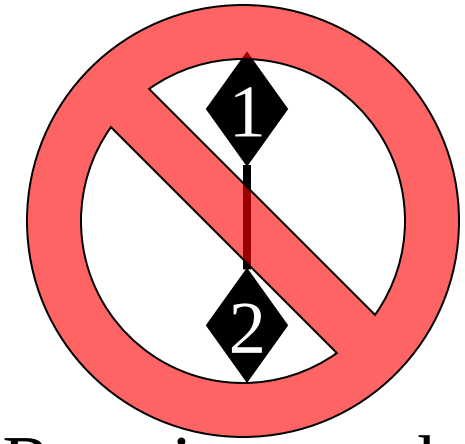
Unipartite projections lose too much.

$$S_1 + ATP \rightarrow S_2 + ADP$$
$$S_3 + ATP \rightarrow S_4 + ADP$$



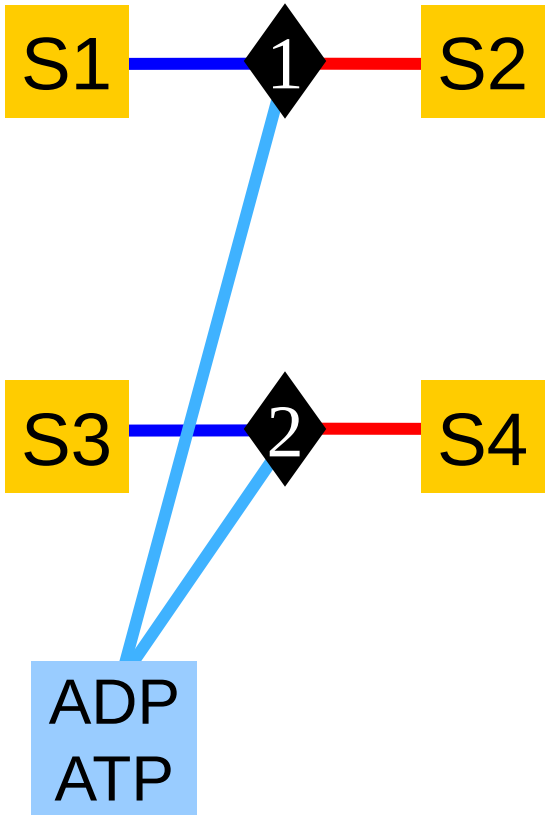
Substrate graph





Reaction graph

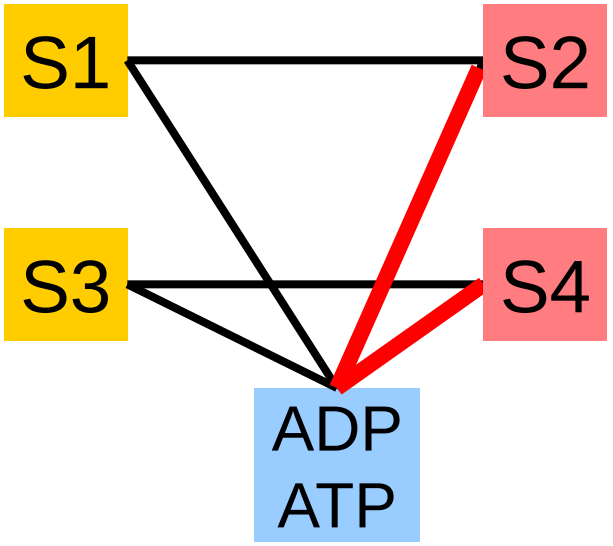
Suppose these reactions are in different modules, say,



Lipid biosyn

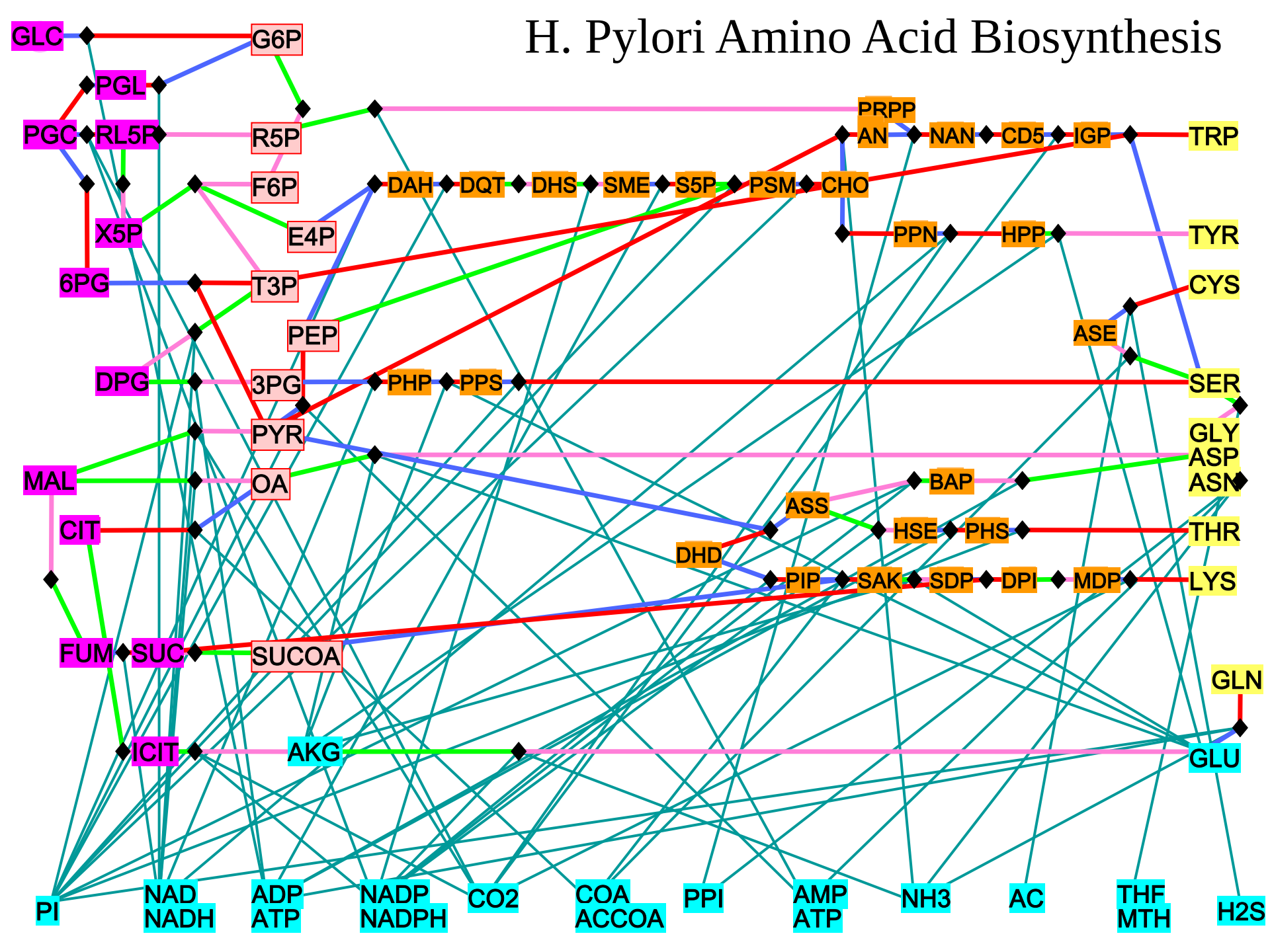
AA biosyn

Substrate graph



“Small world?”

Not really.


H. Pylori Amino Acid Biosynthesis
GLC
G6P
PGL
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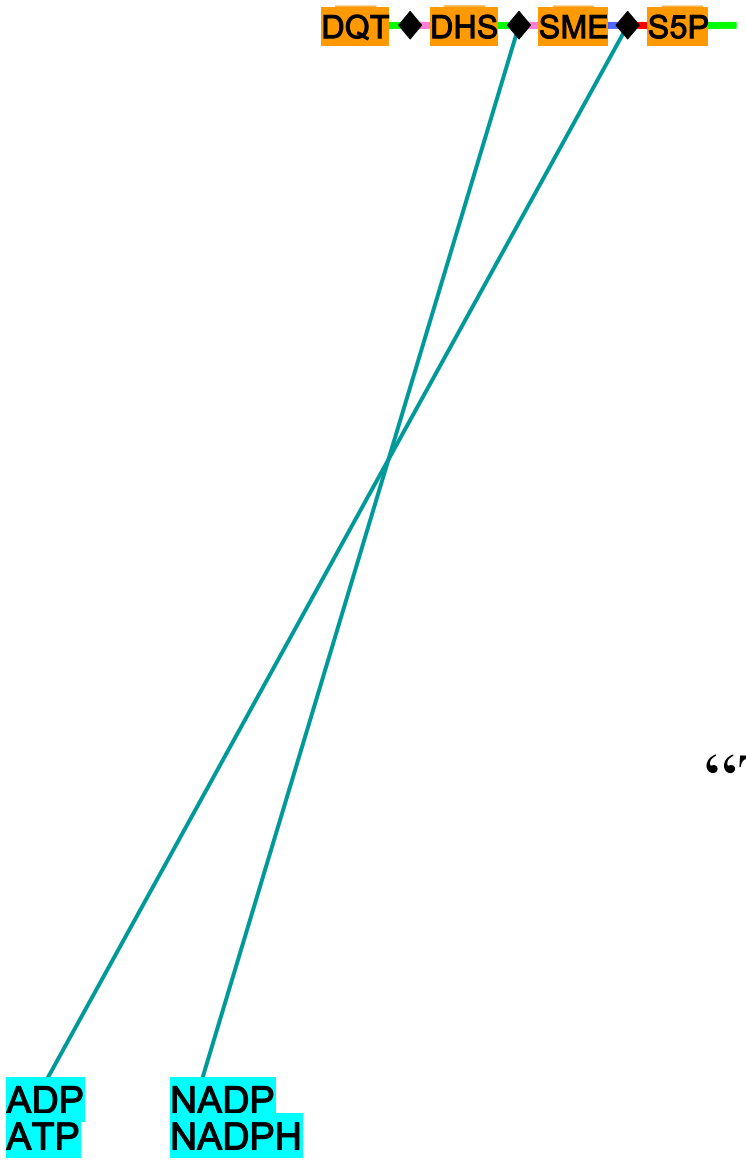
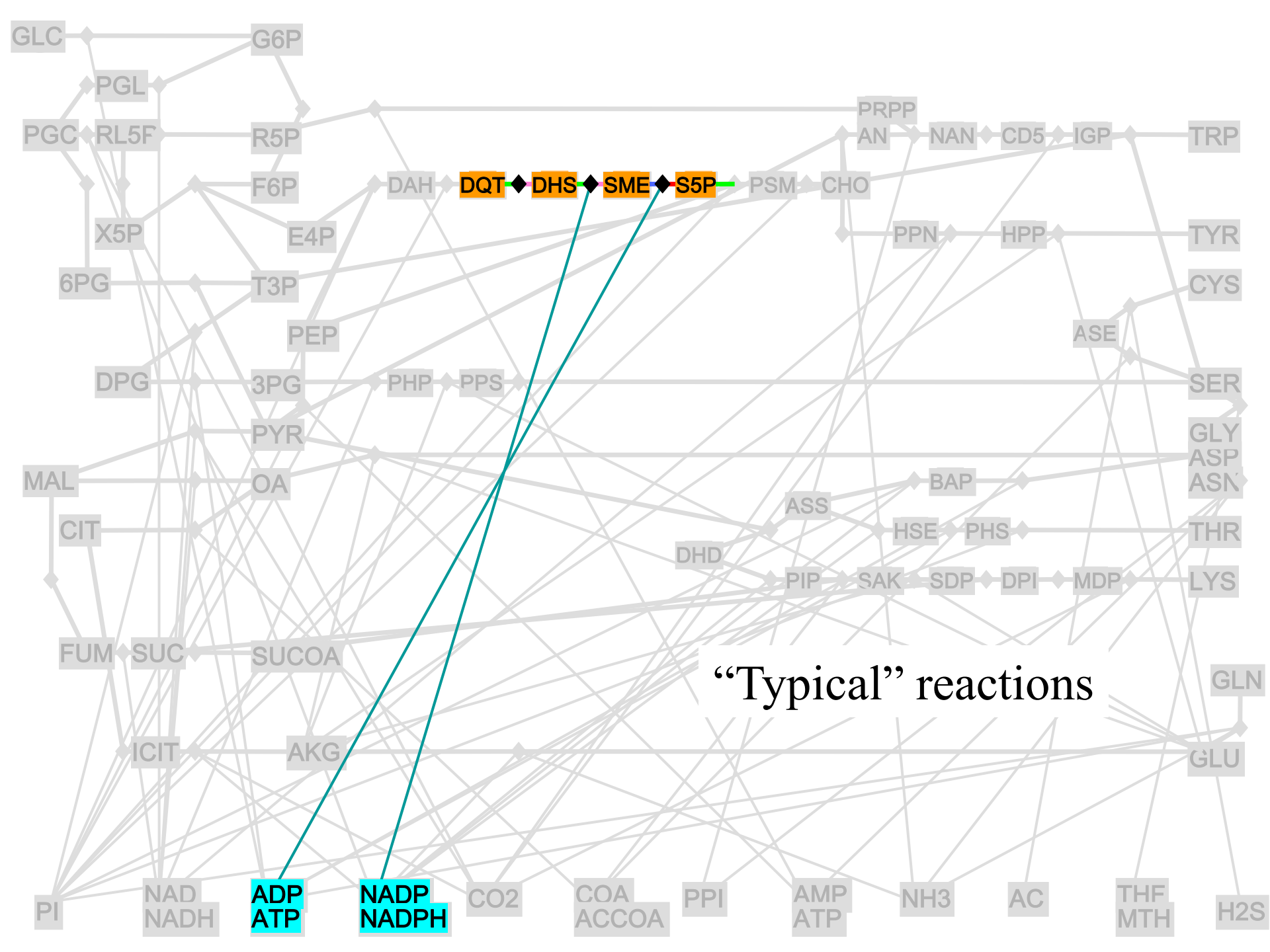
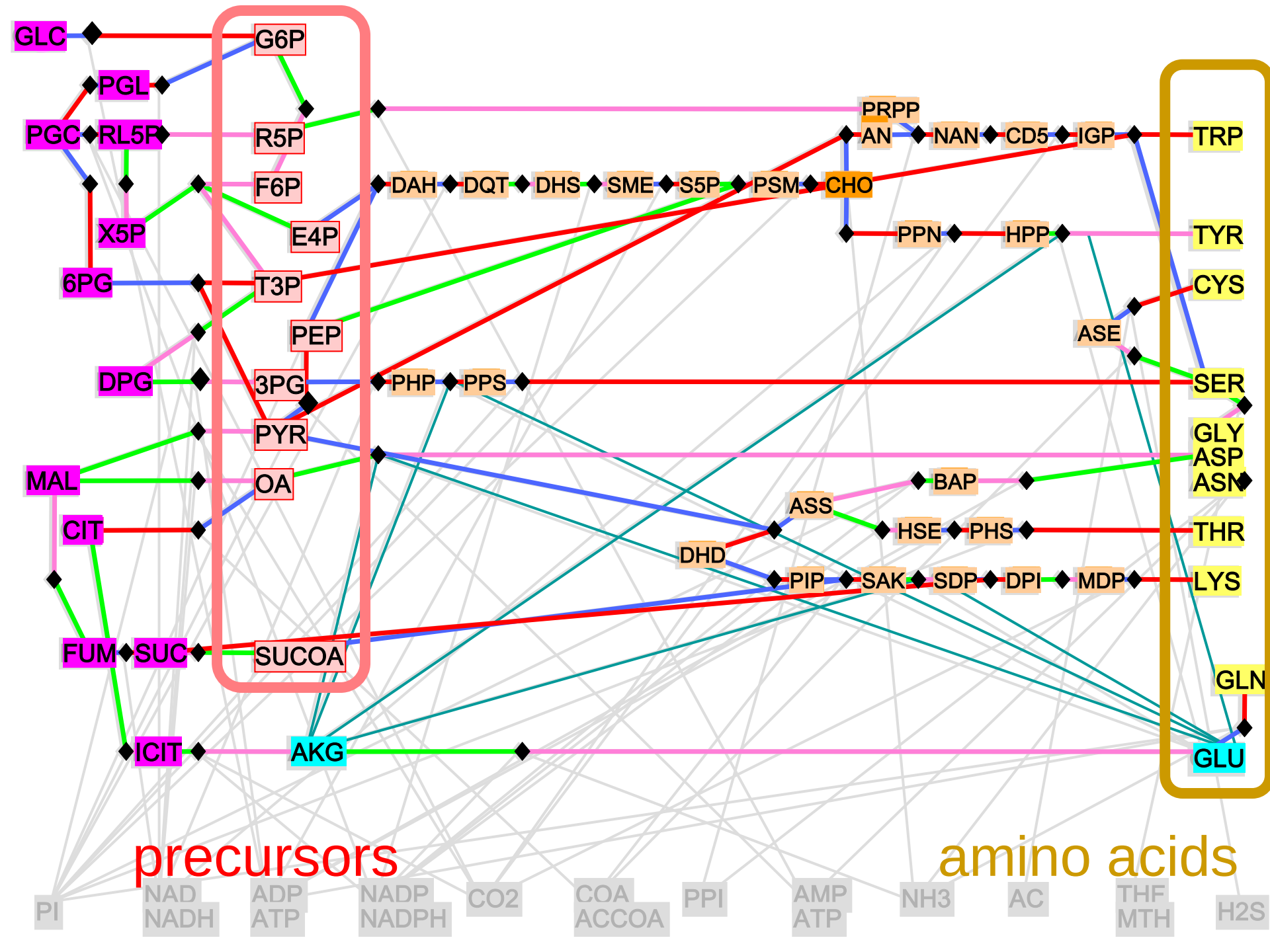
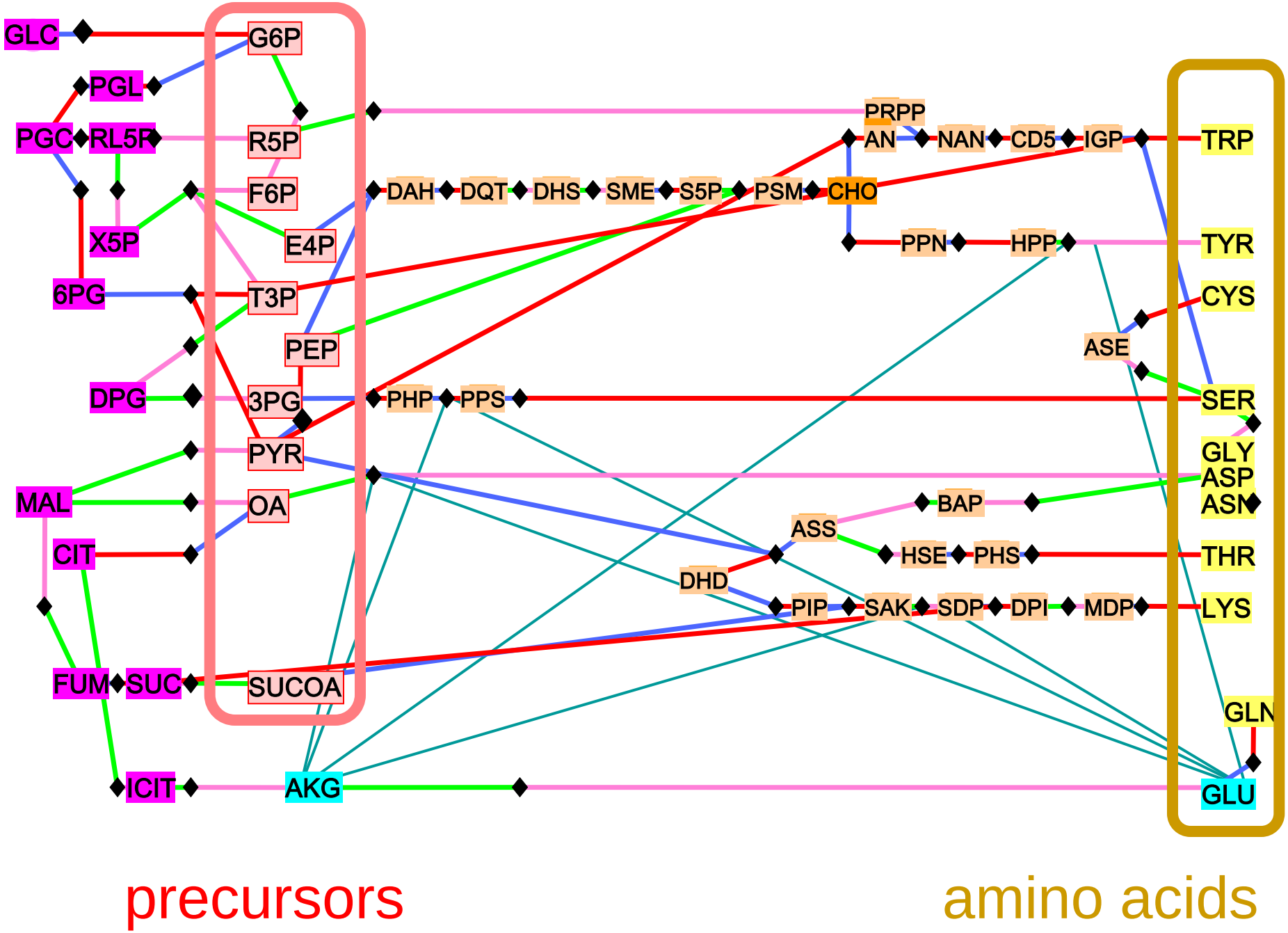
X5P
E4P
6PG
T3P
PEP
DPG
3PG
PYR
MAL
OA
CIT
FUM
SUC
SUCOA
ICIT
AKG
PRPP
AN
NAN
CD5
IGP
TRP
DAH
DQT
DHS
SME
S5P
PSM
CHO
PPN
HPP
TYR
CYS
ASE
PHP
PPS
SER
GLY
ASP
ASN
BAP
ASS
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
GLN
GLU
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S

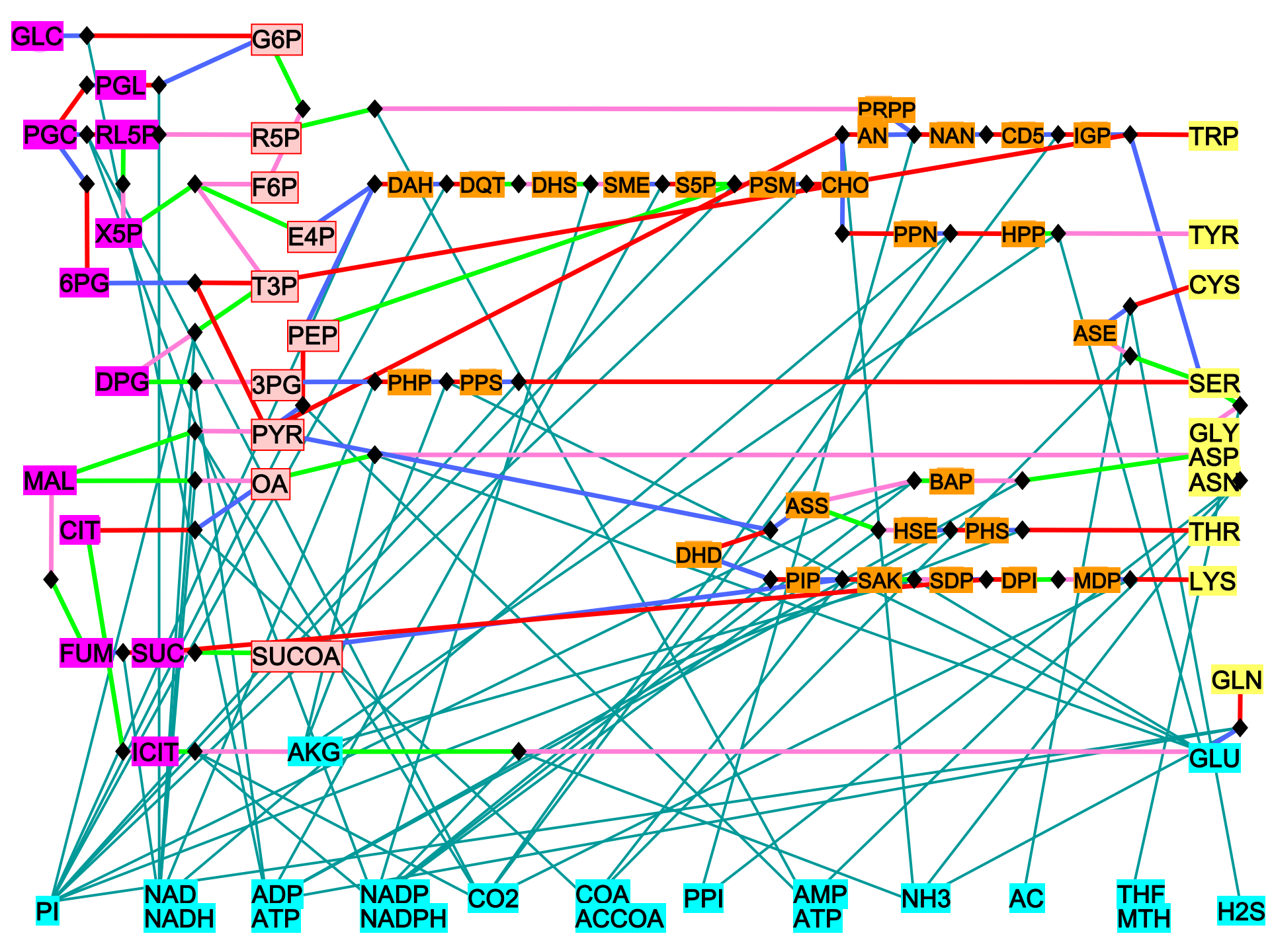


“Typical” reactions


GLC
G6P
PGL
PGC
RL5F
R5P
PRPP
AN
NAN
CD5
IGP
TRP
F6P
DAH
DQT
DHS
SME
S5P
PSM
CHO
X5P
E4P
PPN
HPP
TYR
6PG
T3P
CYS
PEP
ASE
DPG
3PG
PHP
PPS
SER
PYR
GLY
ASP
MAL
OA
BAP
ASN
ASS
CIT
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
FUM
SUC
SUCOA
GLN
ICIT
AKG
GLU
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S
"Typical" reactions


GLC
G6P
PGL
PGC
RL5P
R5P
F6P
X5P
E4P
6PG
T3P
PEP
DPG
3PG
PYR
MAL
OA
CIT
FUM
SUC
SUCOA
ICIT
AKG
PRPP
DAH
DQT
DHS
SME
S5P
PSM
CHO
AN
NAN
CD5
IGP
TRP
PPN
HPP
TYR
CYS
ASE
SER
PHP
PPS
GLY
ASP
ASN
BAP
ASS
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
GLN
GLU
precursors
amino acids
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S

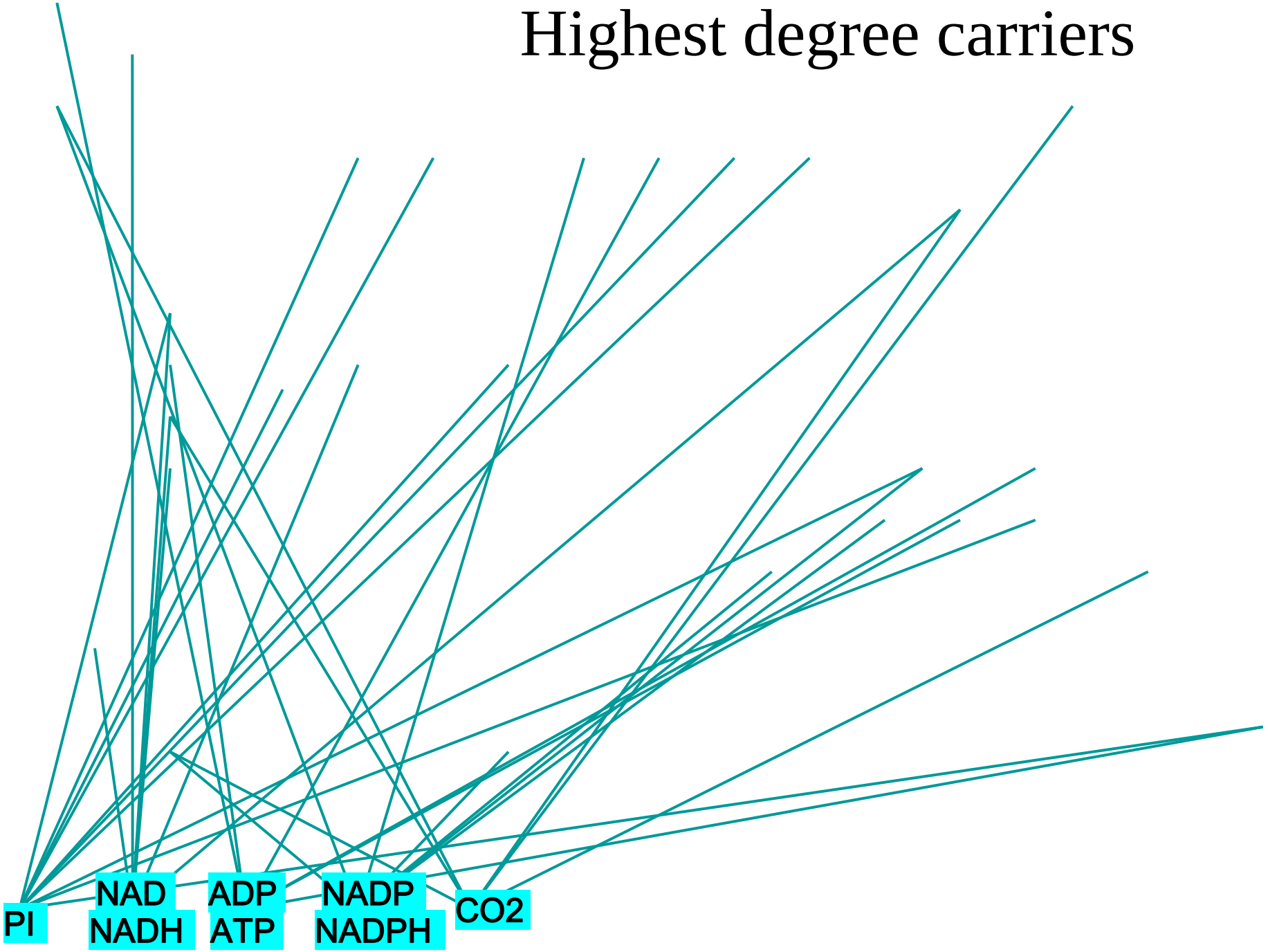

GLC
G6P
PGL
PGC
RL5P
R5P
F6P
X5P
E4P
6PG
T3P
PEP
DPG
3PG
PYR
MAL
OA
CIT
FUM
SUC
SUCOA
ICIT
AKG
PRPP
DAH
DQT
DHS
SME
S5P
PSM
CHO
AN
NAN
CD5
IGP
TRP
PPN
HPP
TYR
CYS
ASE
SER
PHP
PPS
GLY
ASP
ASN
BAP
ASS
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
GLN
GLU
precursors
amino acids


GLC
G6P
PGL
PGC
RL5R
R5P
PRPP
AN
NAN
CD5
IGP
TRP
F6P
DAH
DQT
DHS
SME
S5P
PSM
CHO
X5P
E4P
PPN
HPP
TYR
6PG
T3P
CYS
PEP
ASE
DPG
3PG
PHP
PPS
SER
PYR
GLY
ASP
MAL
OA
BAP
ASN
ASS
CIT
HSE
PHS
THR
DHD
PIP
SAK
SDP
DPI
MDP
LYS
FUM
SUC
SUCOA
GLN
ICIT
AKG
GLU
PI
NAD
NADH
ADP
ATP
NADP
NADPH
CO2
COA
ACCOA
PPI
AMP
ATP
NH3
AC
THF
MTH
H2S

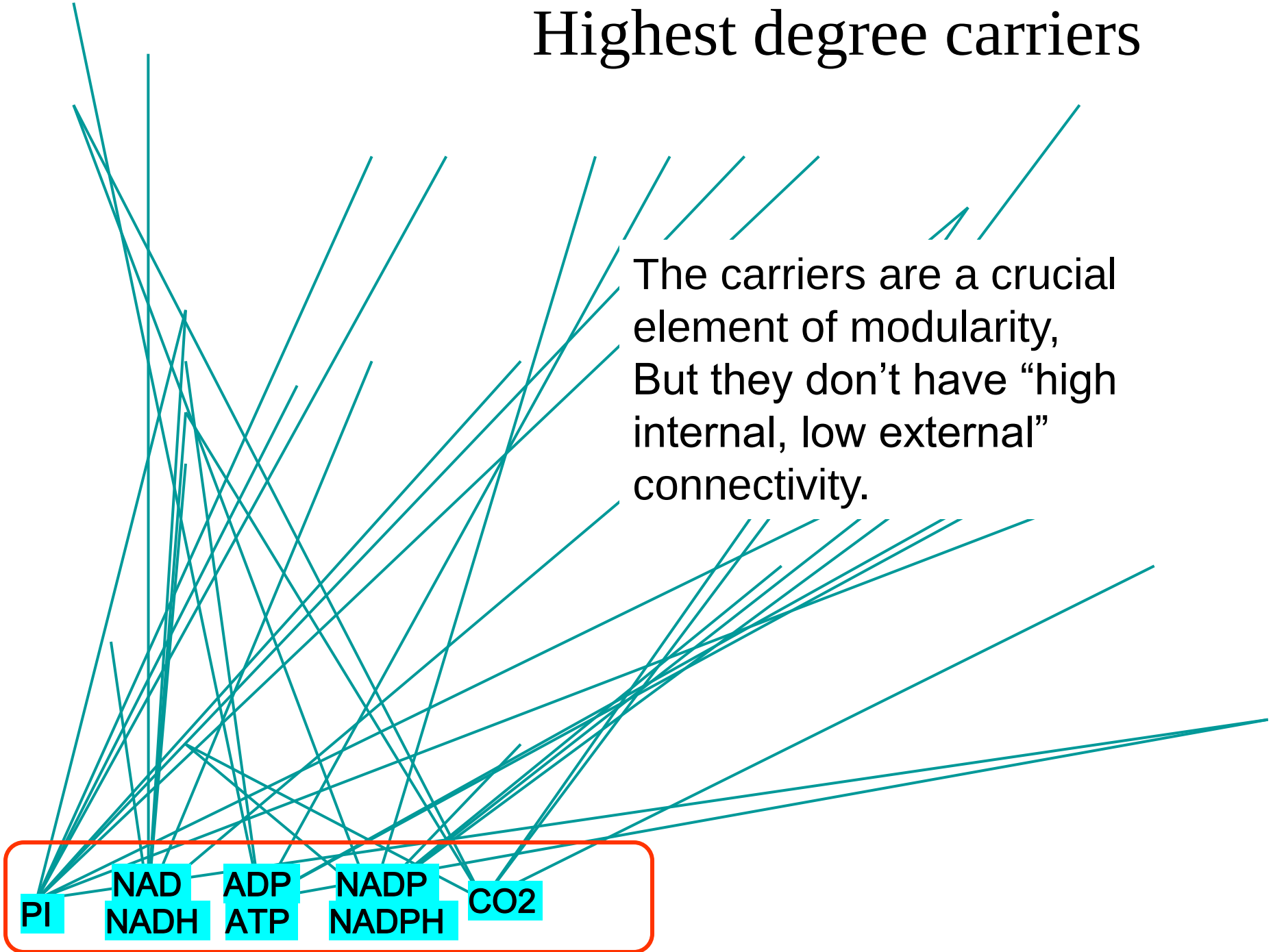
Aside

- A popular view of “modularity” is
  - High connectivity within the module
  - Low connectivity to the outside
- This is intuitively appealing, and there are some examples…
- …but the most important elements of biological modularity are often exactly the opposite of this

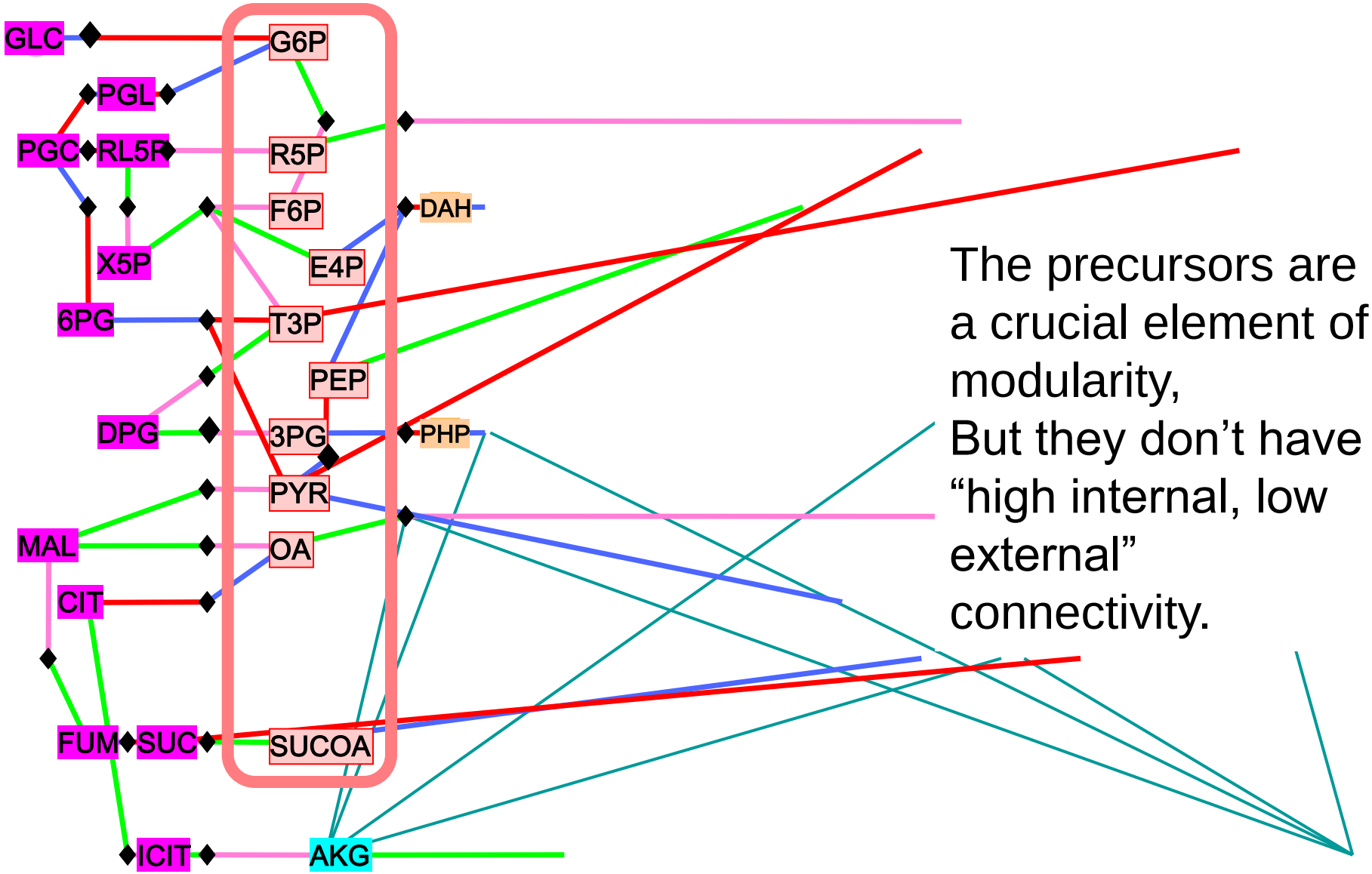
Highest degree carriers



Highest degree carriers



The carriers are a crucial element of modularity,
But they don't have "high internal, low external" connectivity.

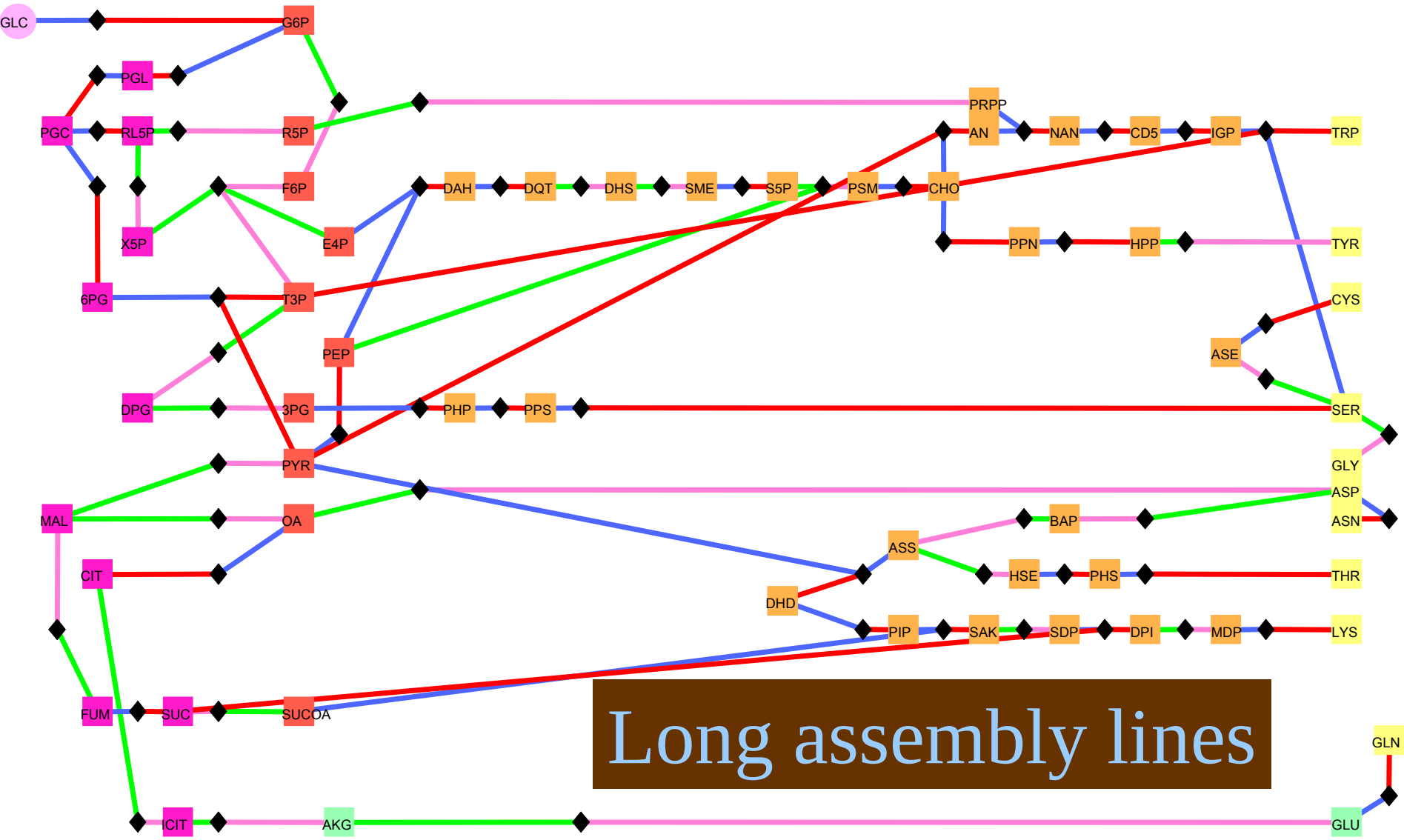


The precursors are a crucial element of modularity,
But they don't have "high internal, low external" connectivity.

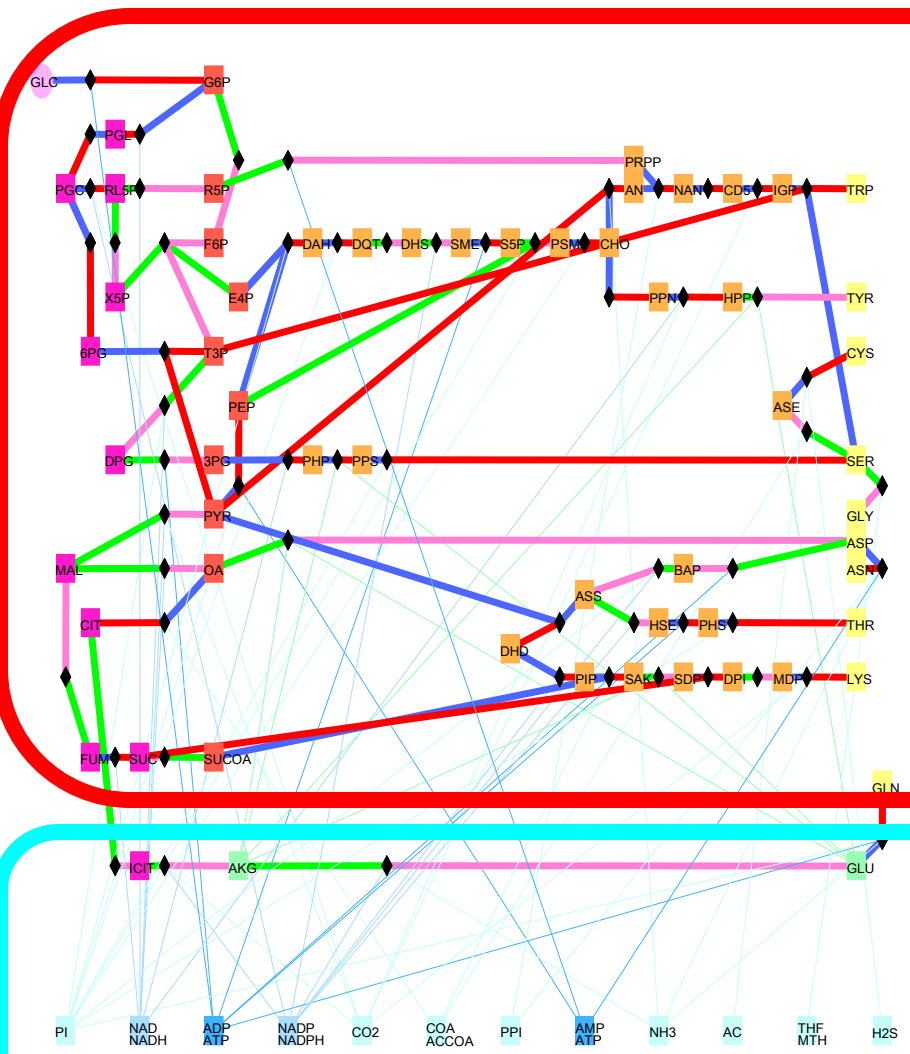
precursors

Without carriers

“long” not “small” worlds

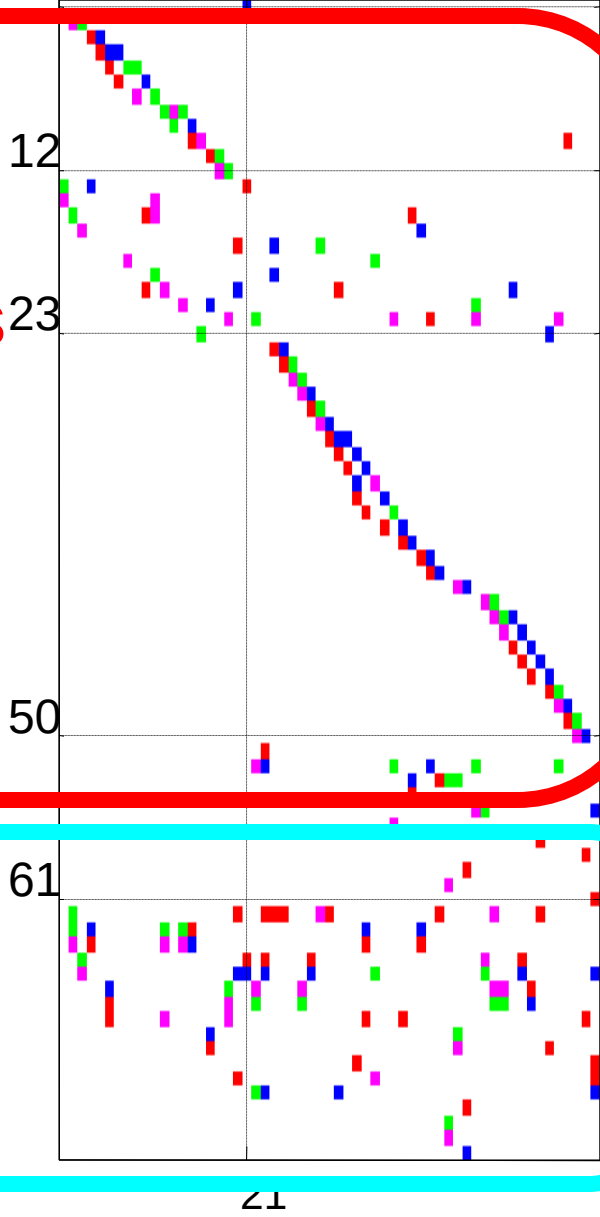


Long assembly lines



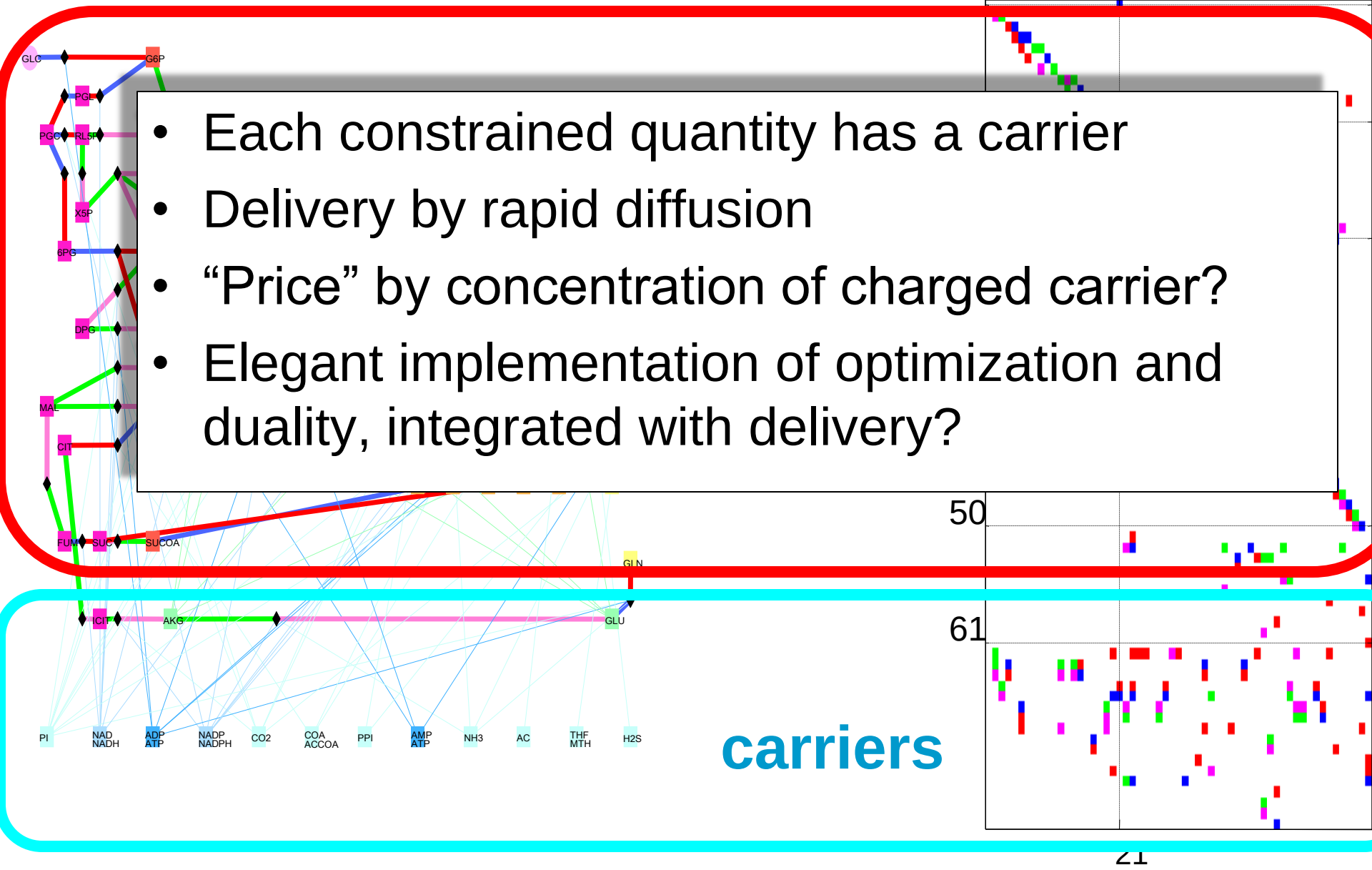
metabolites

carriers



reactions

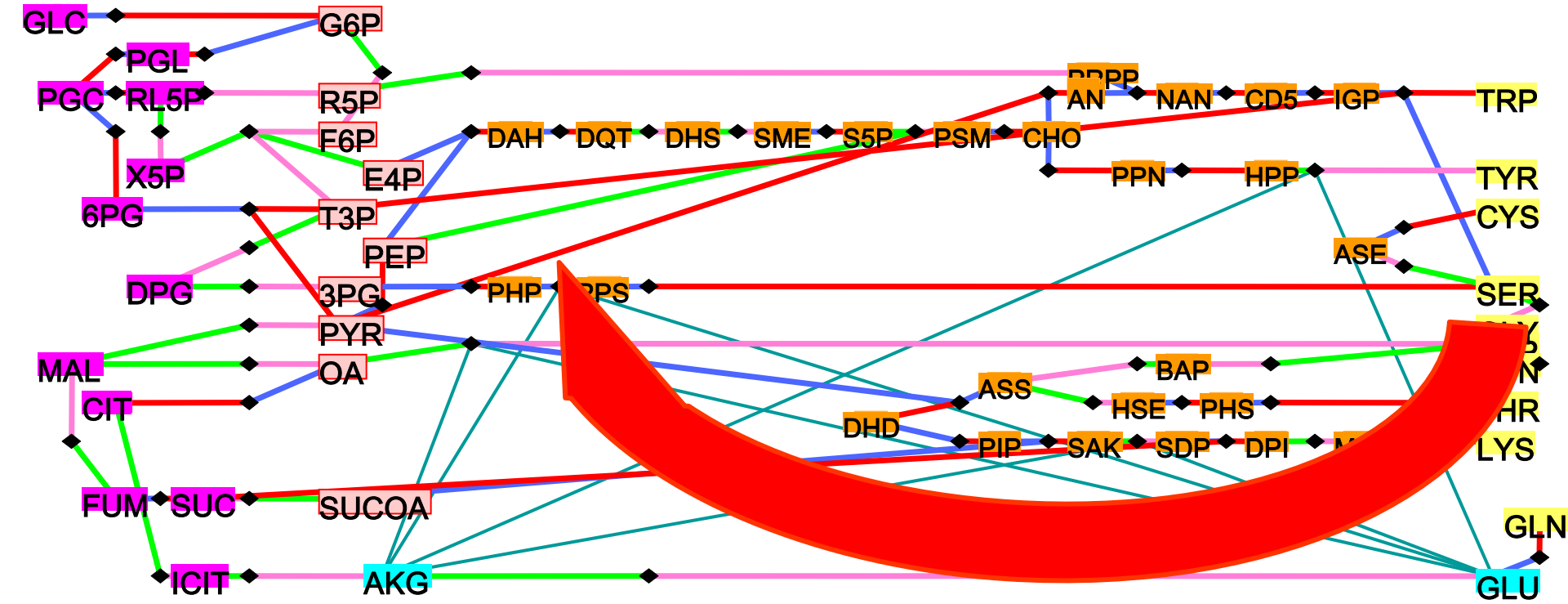
“Vertical” decomposition



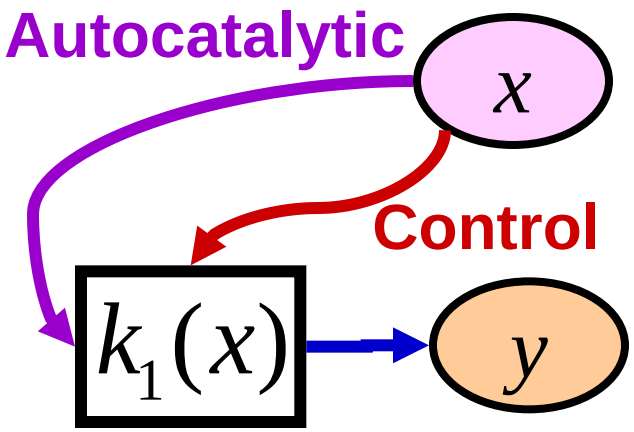
- Each constrained quantity has a carrier
- Delivery by rapid diffusion
- “Price” by concentration of charged carrier?
- Elegant implementation of optimization and duality, integrated with delivery?

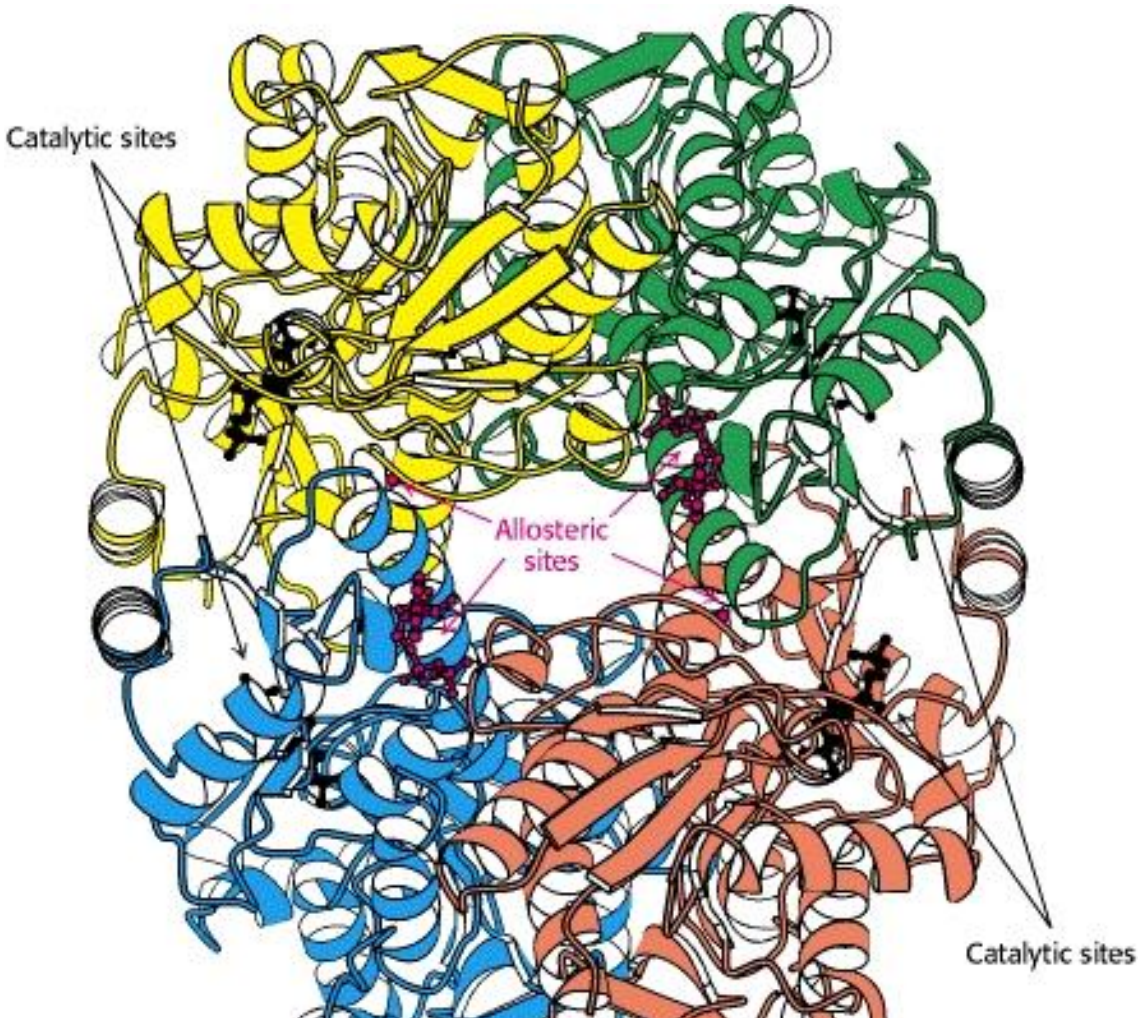
carriers

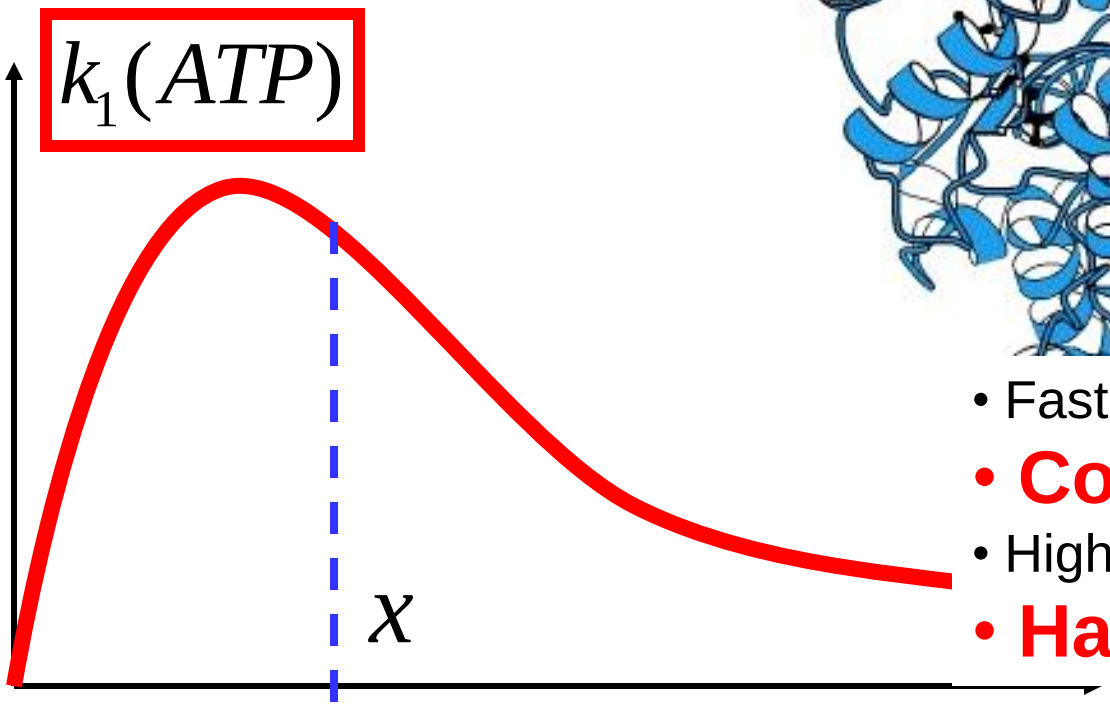
Prices?



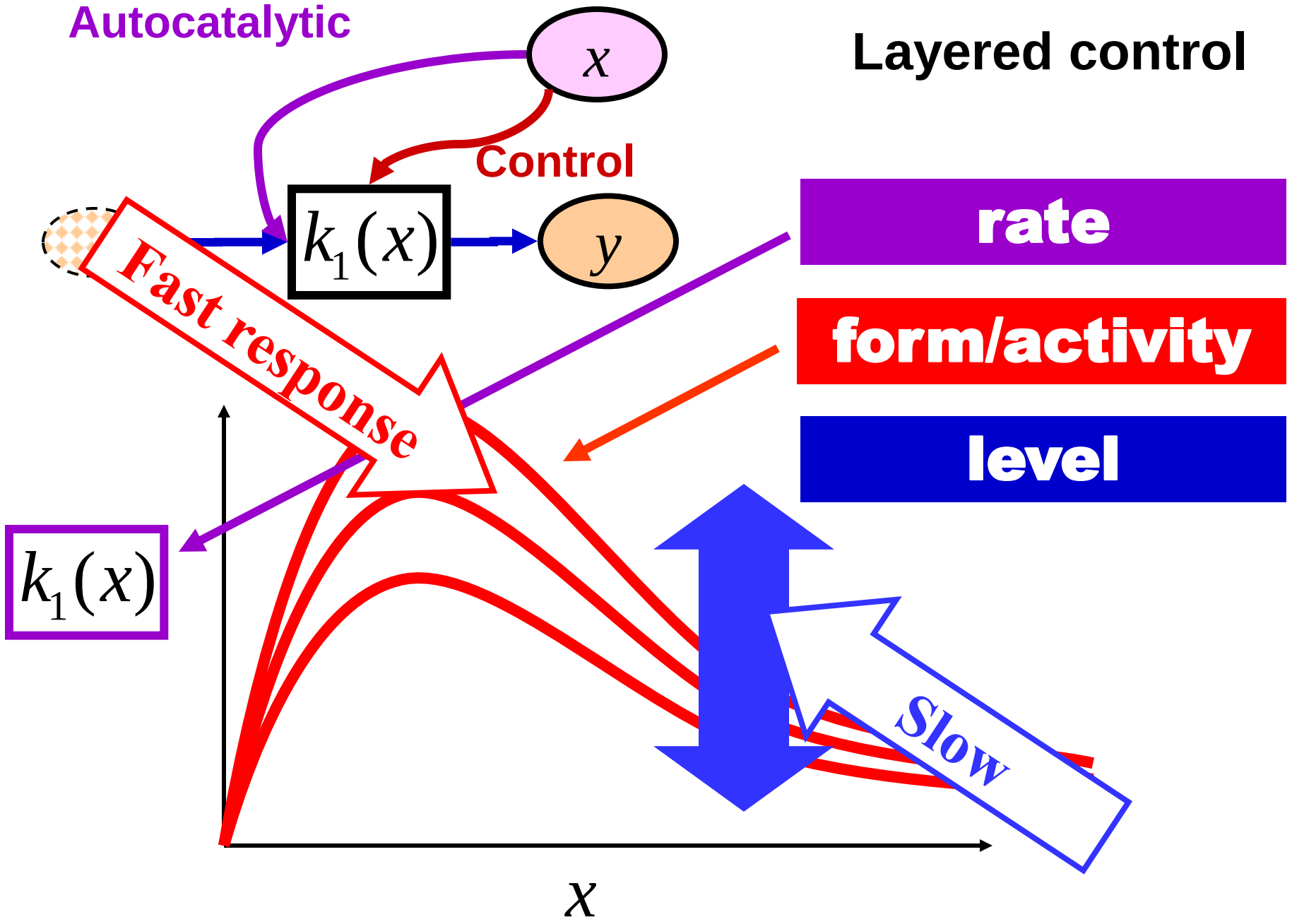
- Fastest allosteric feedback control
- Complex proteins
- High metabolic overhead
- Hard to reprogram





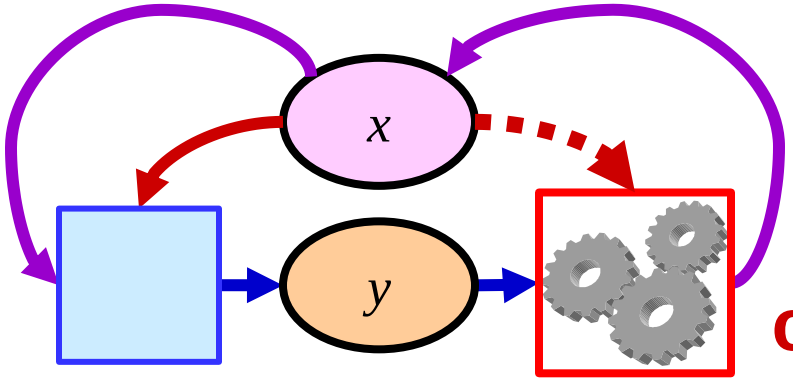


- Fastest allosteric feedback control
- **Complex proteins**
- High metabolic overhead
- **Hard to reprogram**



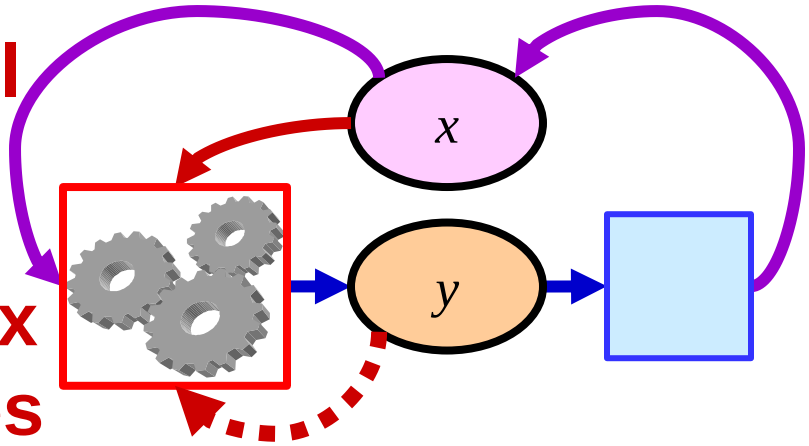
Layered control

- How to get rid of the RHP zero?
- What are the new tradeoffs?

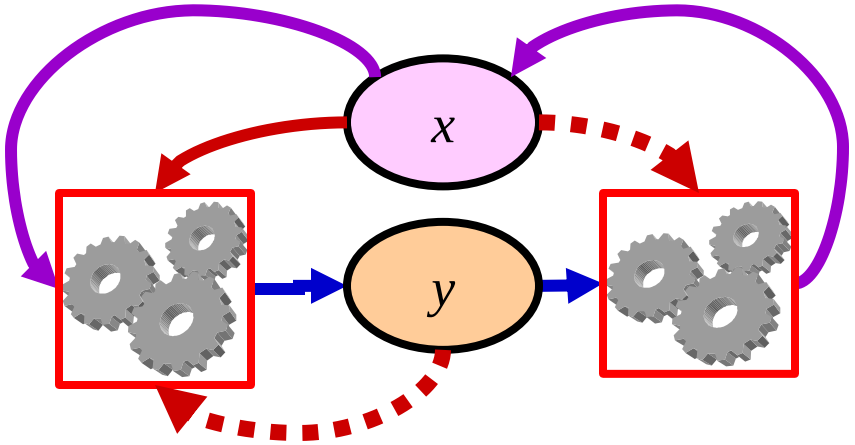


More control

More complex enzymes

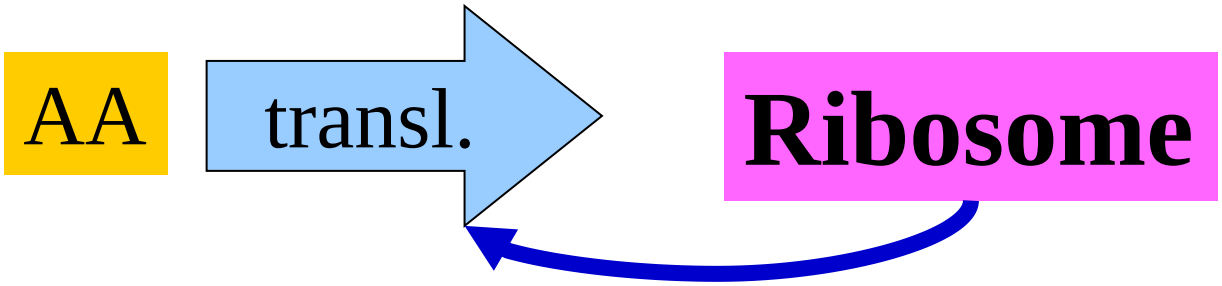


Biology appears to do both



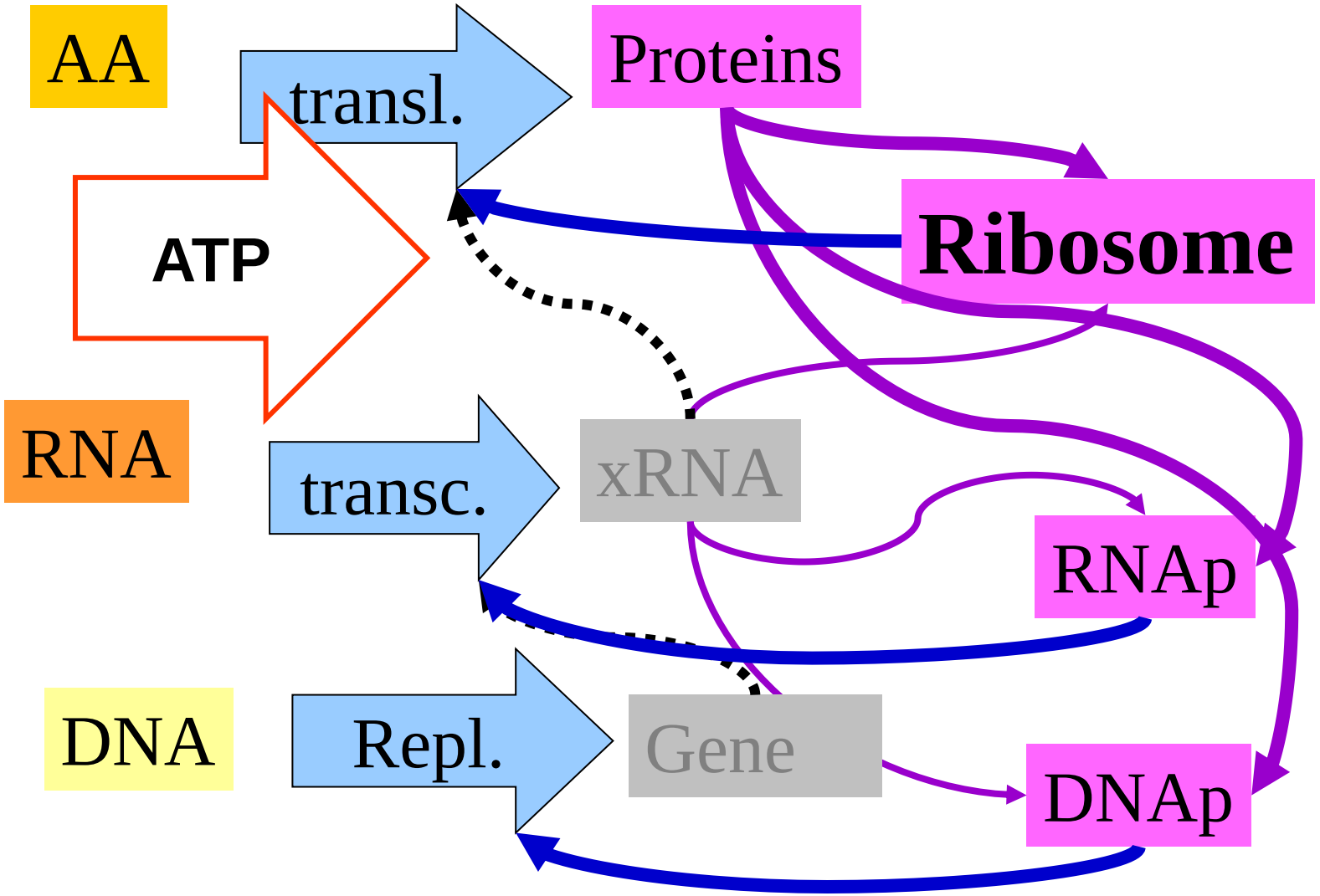
Lower layer autocatalysis

Ribosomes making ribosomes



Lower layer autocatalysis

Macromolecules making …



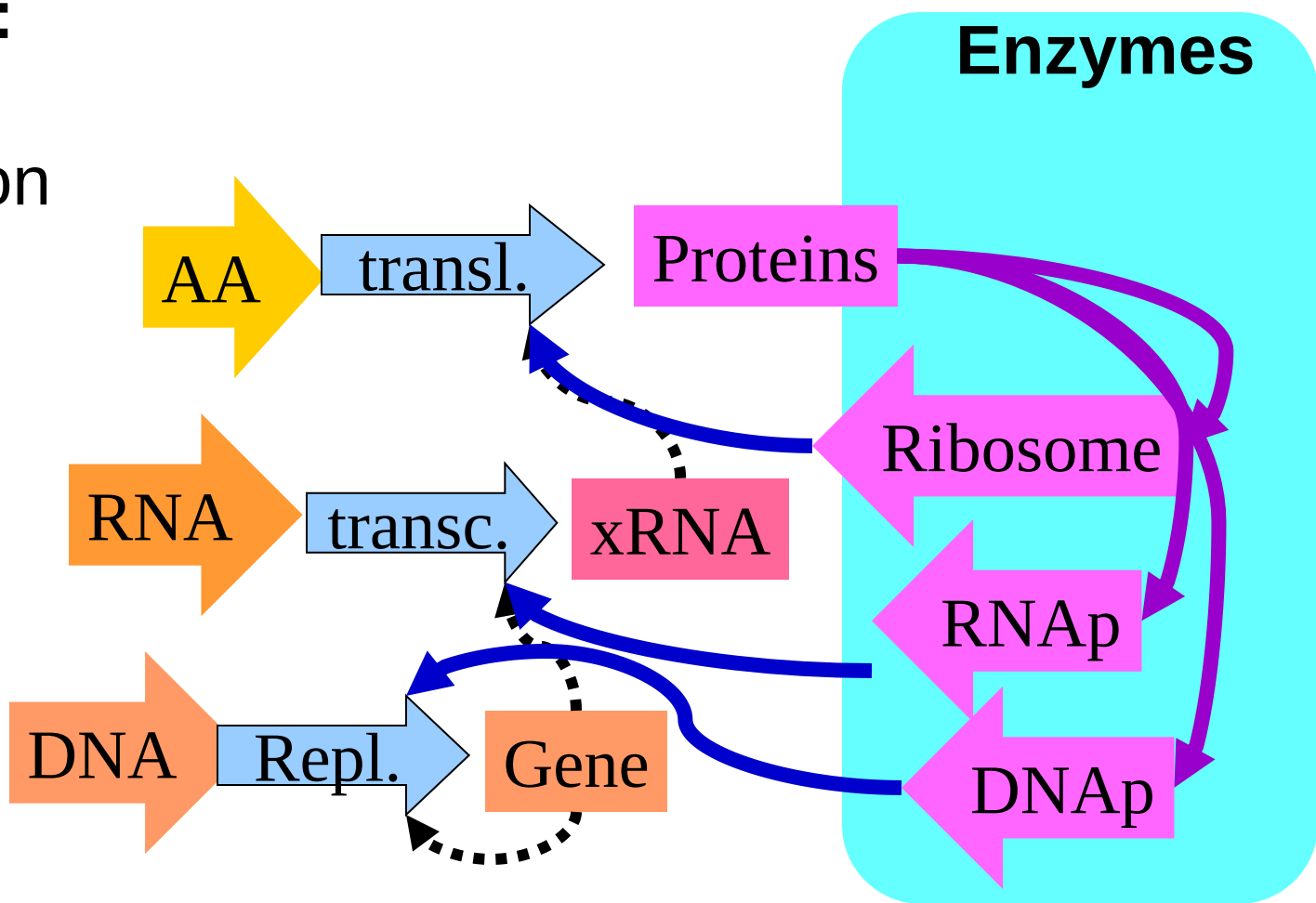
Autocatalytic within lower layers

- Collectively self-replicating
- Ribosomes make ribosomes, etc

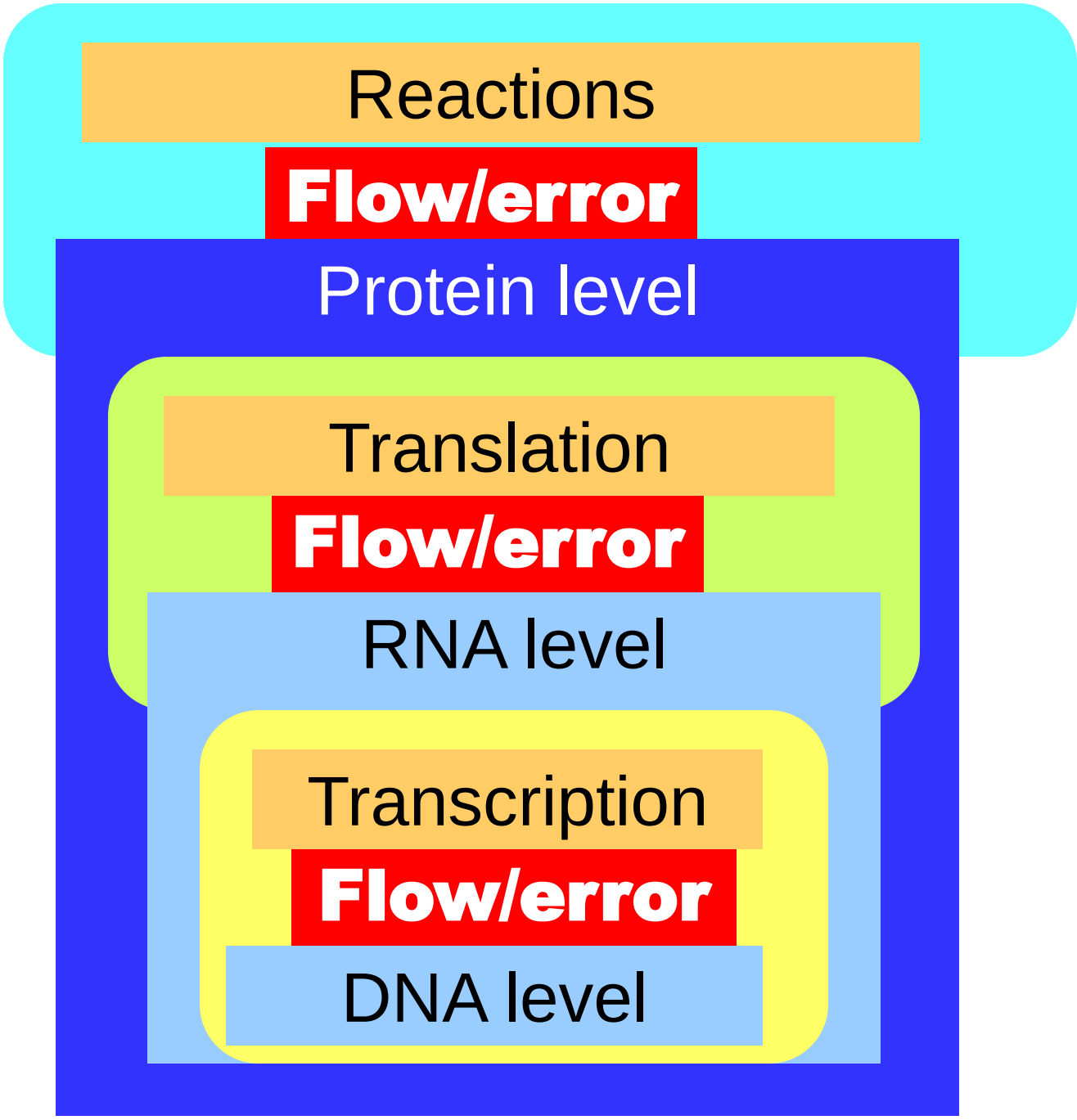
Three lower layers? Yes:

- Translation
- Transcription
- Replication

Naturally recursive



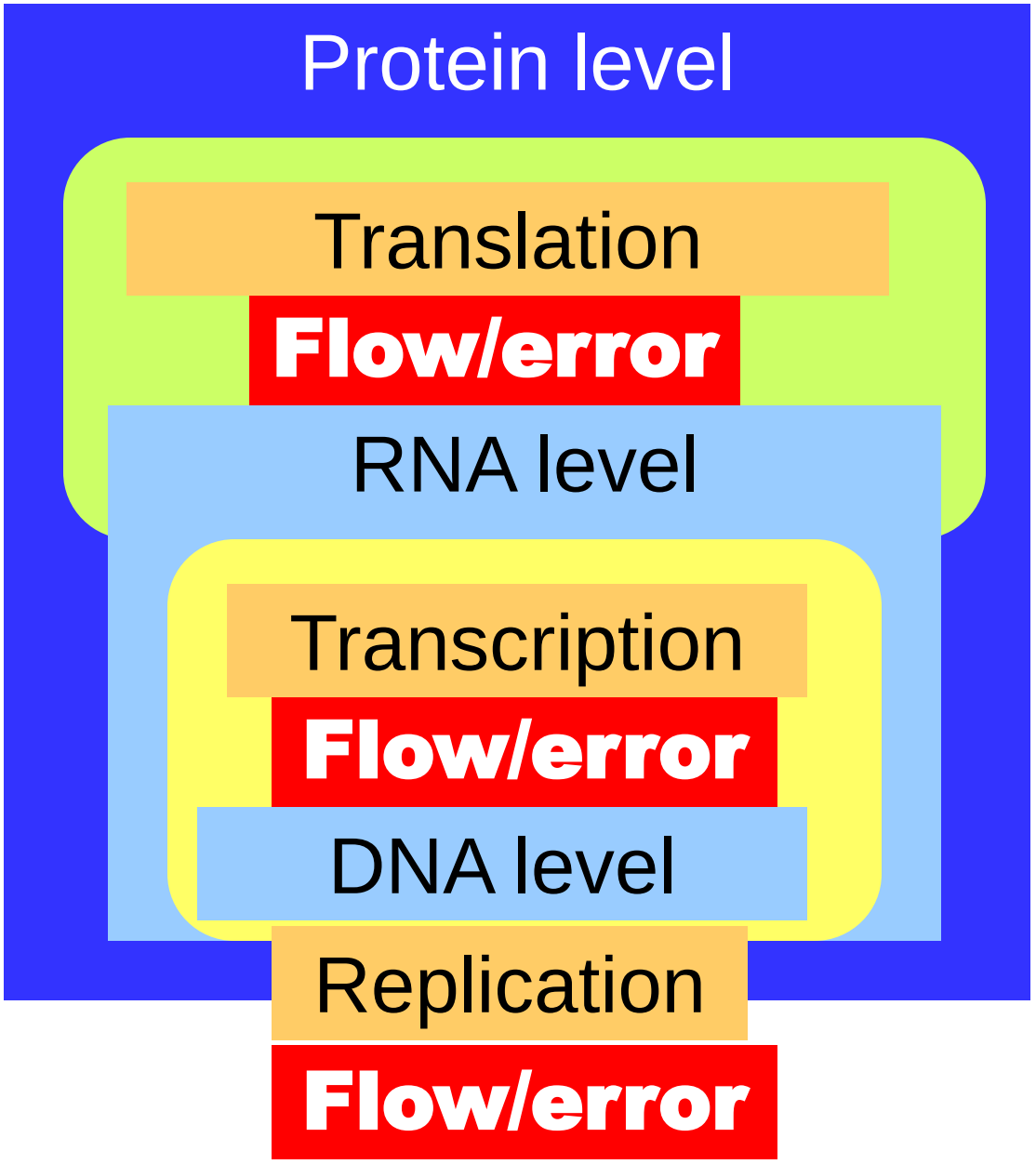
Naturally recursive

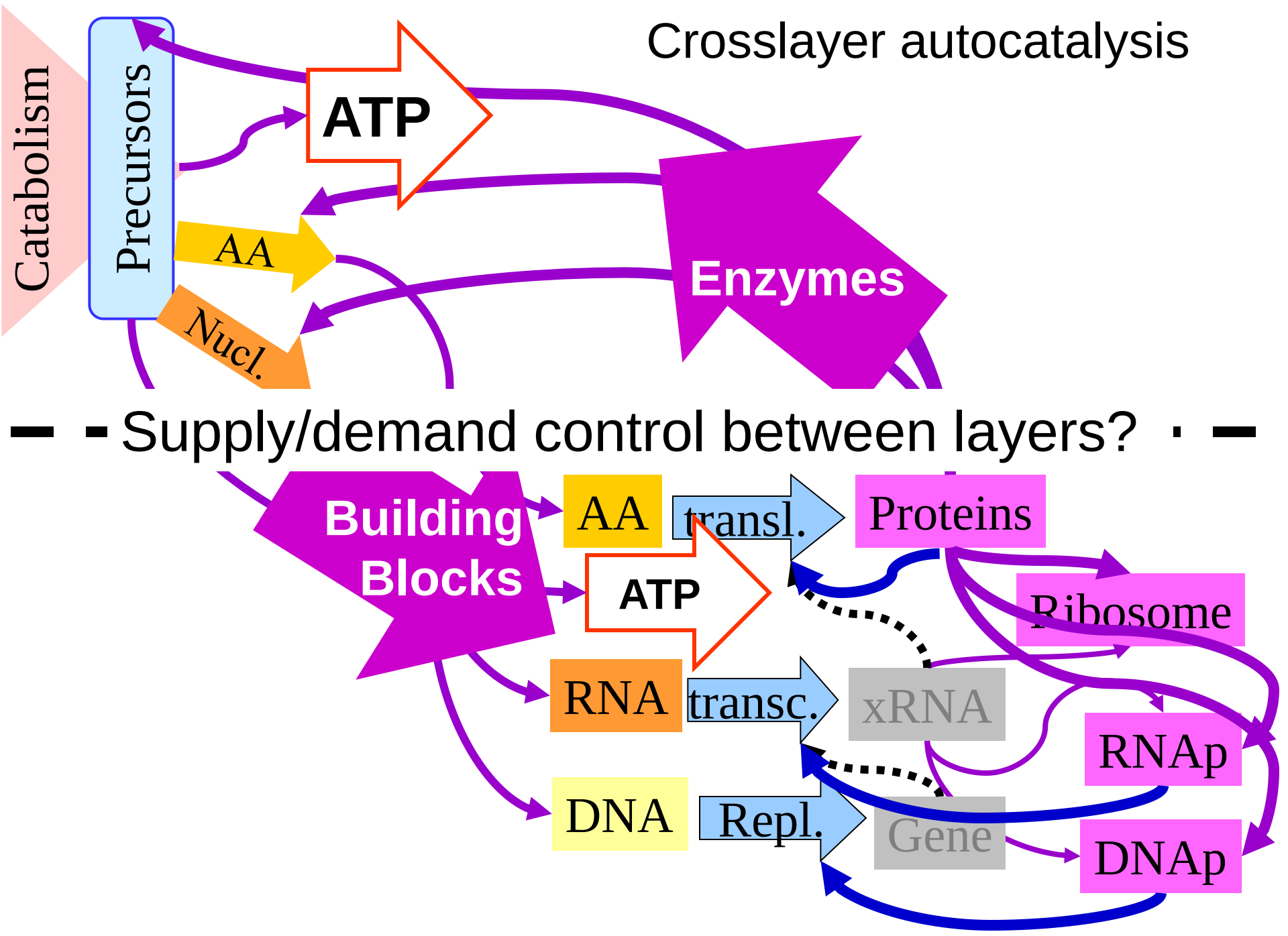


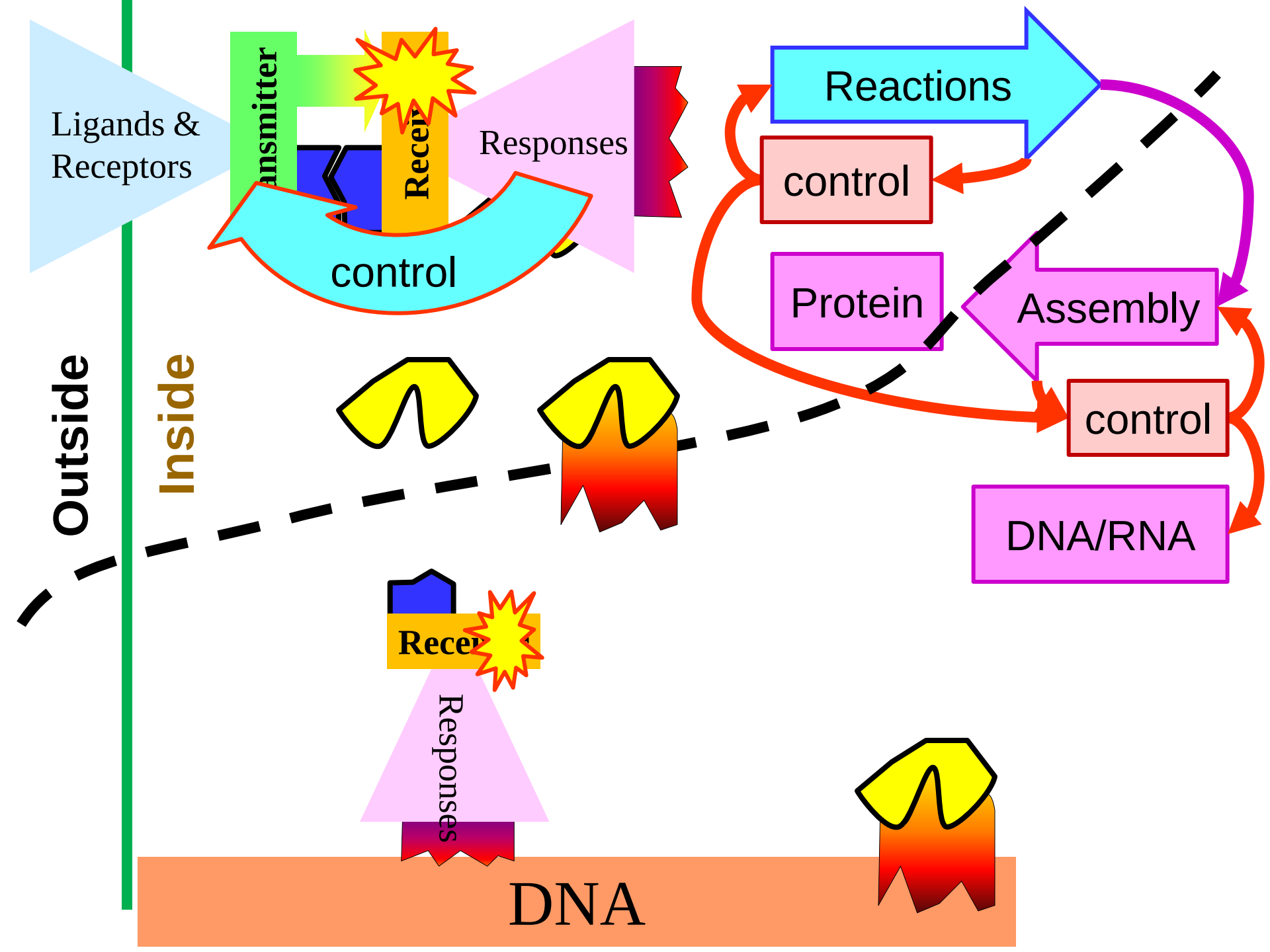
Three lower layers? Yes:

- Translation
- Transcription
- Replication/ rearrangement

DNA Replication/ Rearrangement is complex and highly controlled

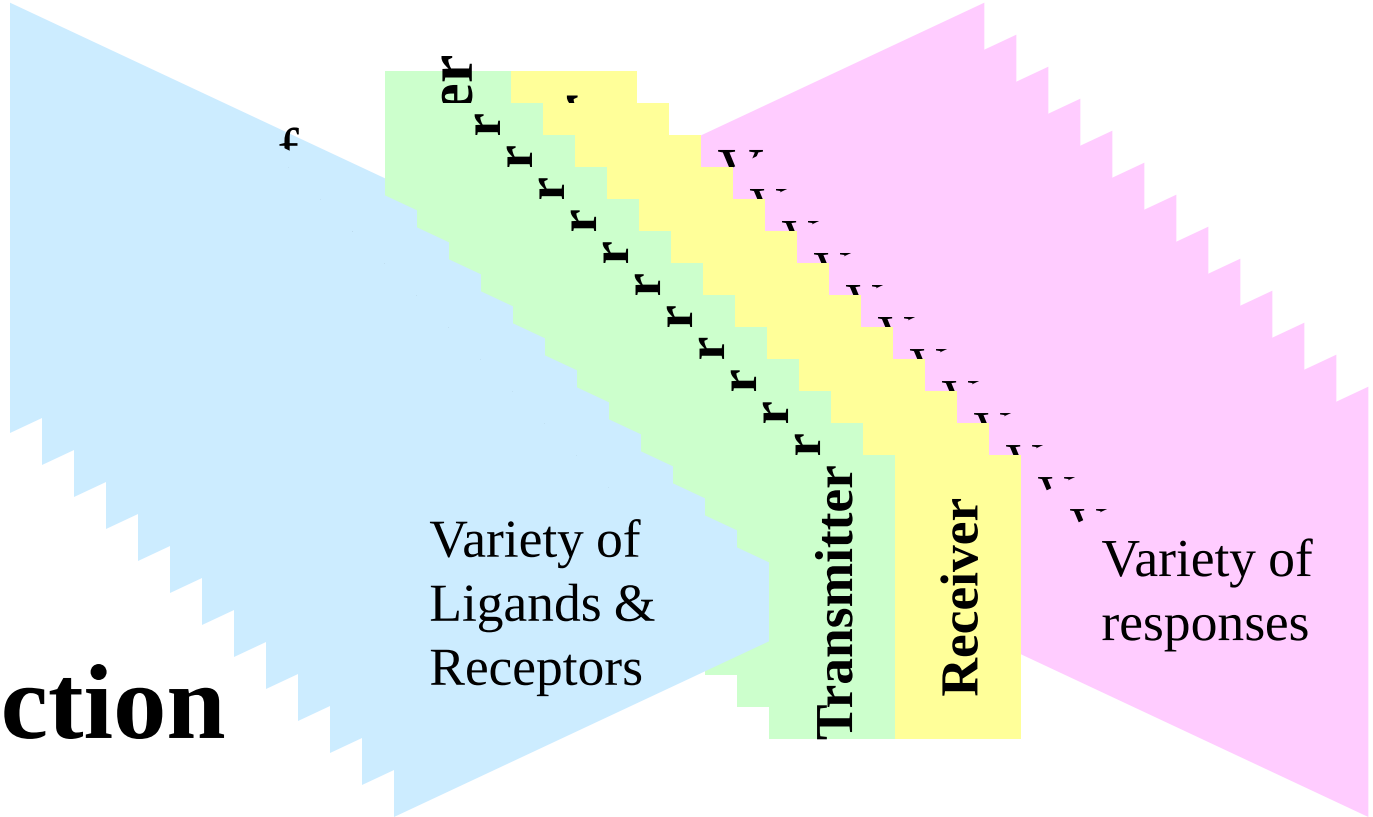


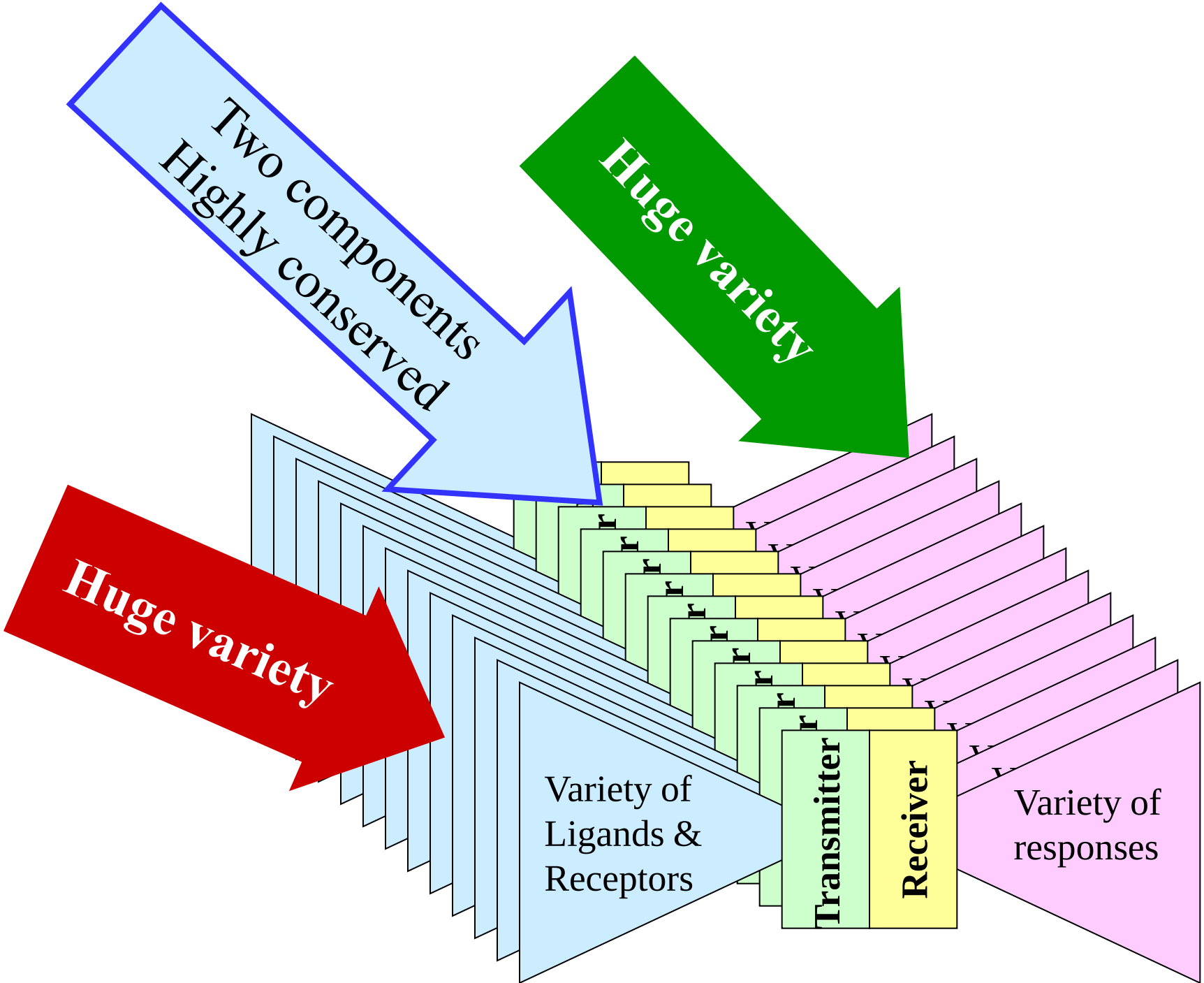

Crosslayer autocatalysis
Catabolism
Precursors
ATP
AA
Nucl.
Enzymes
Supply/demand control between layers?
Building Blocks
AA
transl.
Proteins
ATP
Ribosome
RNA
transc.
xRNA
RNAp
DNA
Repl.
Gene
DNAp

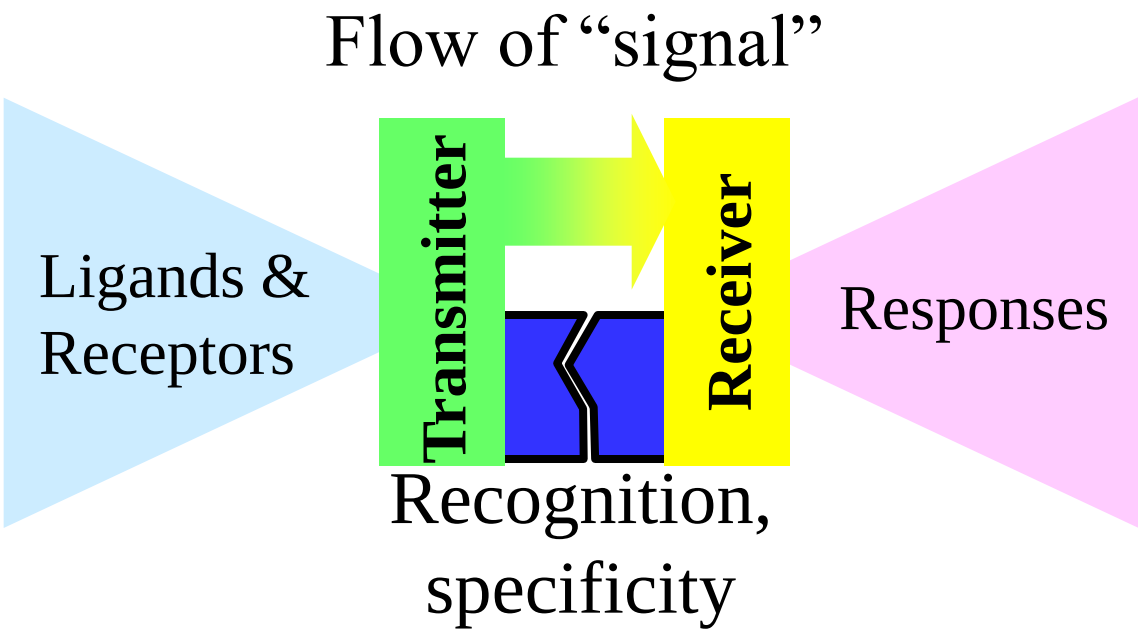

Ligands &
Receptors
Responses
control
Reactions
control
Protein
Assembly
control
DNA/RNA
Outside
Inside
Responses
DNA

- ≈50 such “two component” systems in *E. Coli*
- All use the same protocol
  - Histidine autokinase transmitter
  - Aspartyl phospho-acceptor receiver
- Huge variety of receptors and responses
- Also multistage (phosphorelay) versions

Signal transduction




Two components
Highly conserved
Huge variety
Huge variety
Variety of
Ligands &
Receptors
Transmitter
Receiver
Variety of
responses



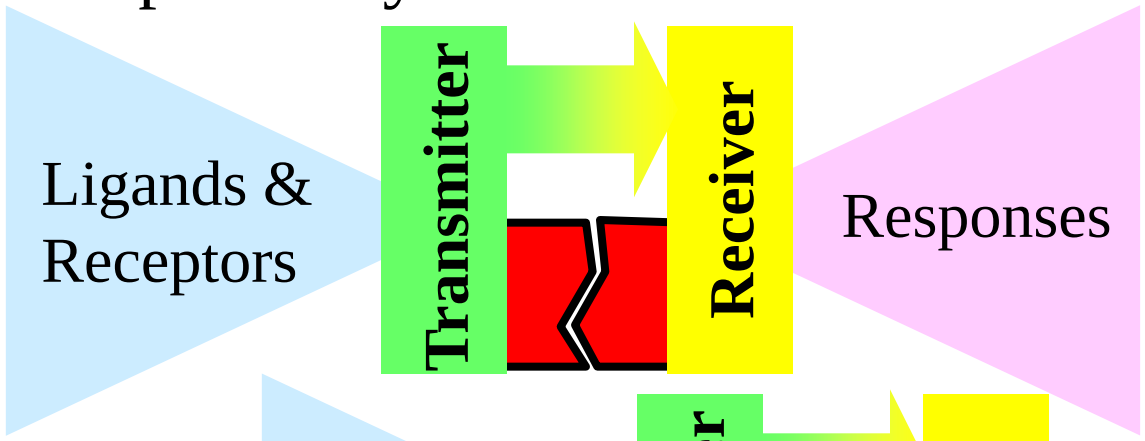
Shared
protocols

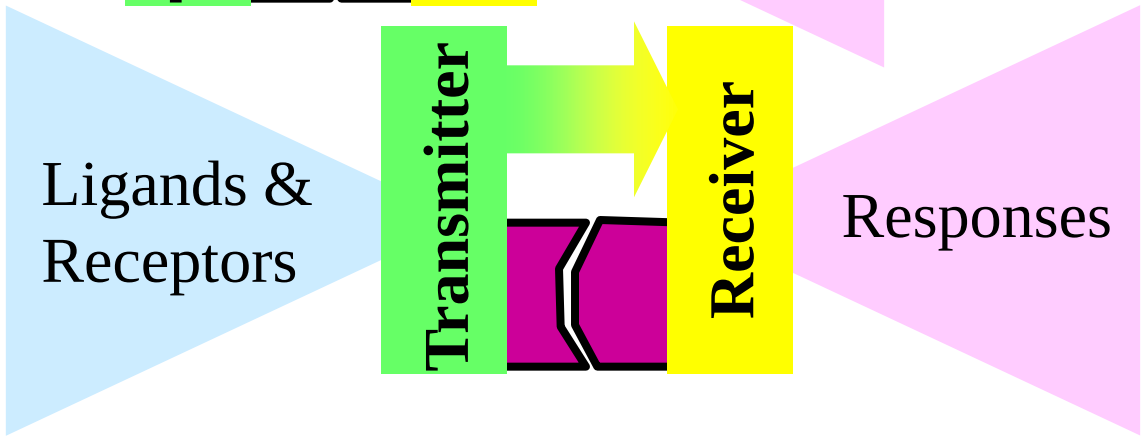
- “Name resolution” within signal transduction
- Transmitter must locate “cognate” receiver and avoid non-cognate receivers
- Global search by rapid, local diffusion
- Limited to very small volumes

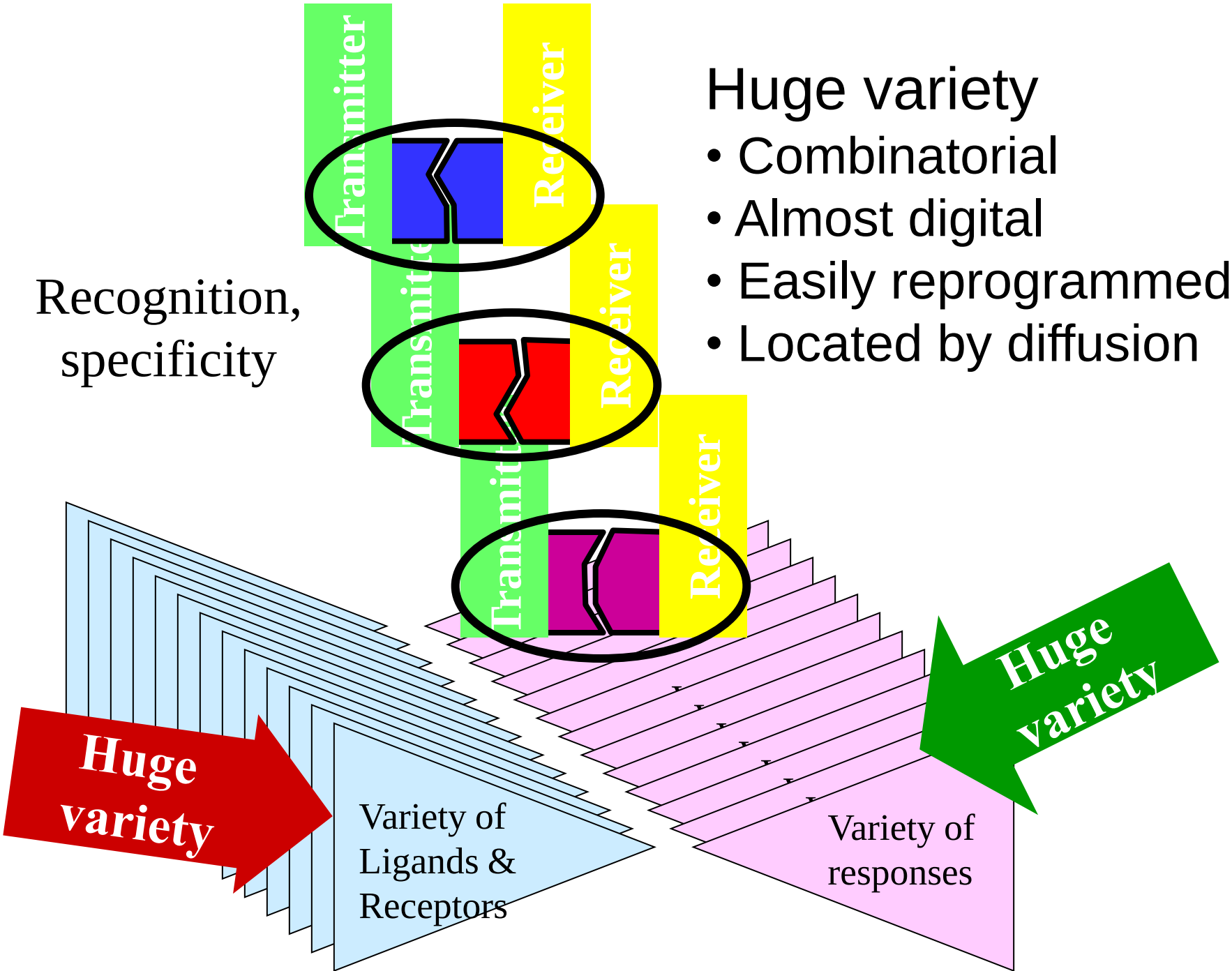
Flow of “signal”

Shared protocols

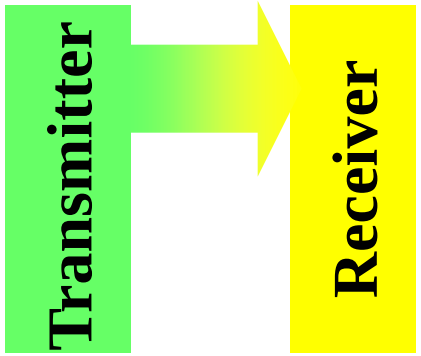
Recognition, specificity





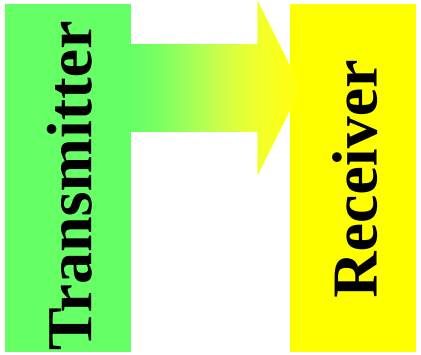

Transmitter
Receiver
Transmitter
Receiver
Transmitter
Receiver
Recognition, specificity
Huge variety
• Combinatorial
• Almost digital
• Easily reprogrammed
• Located by diffusion
Huge variety
Huge variety
Variety of Ligands & Receptors
Variety of responses

Flow of “signal”

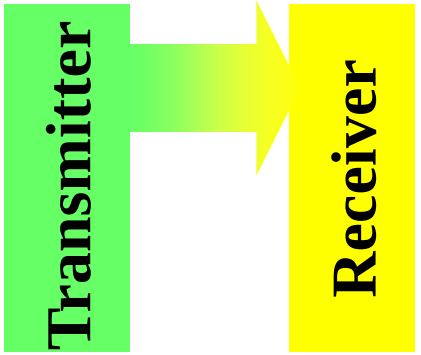


Limited variety

- Fast, analog (via #)
- Hard to change



Reusable in different pathways



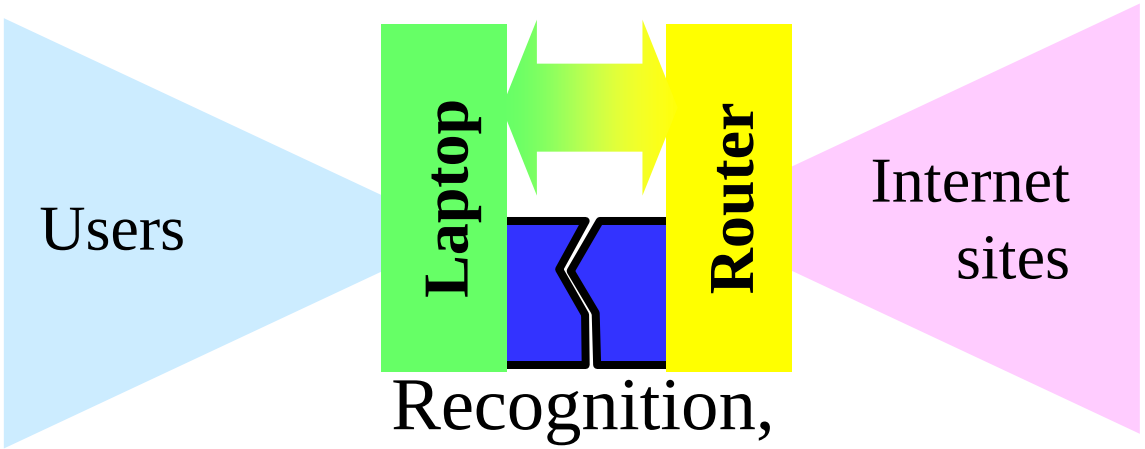
Flow of “signal”

Recognition,
specificity

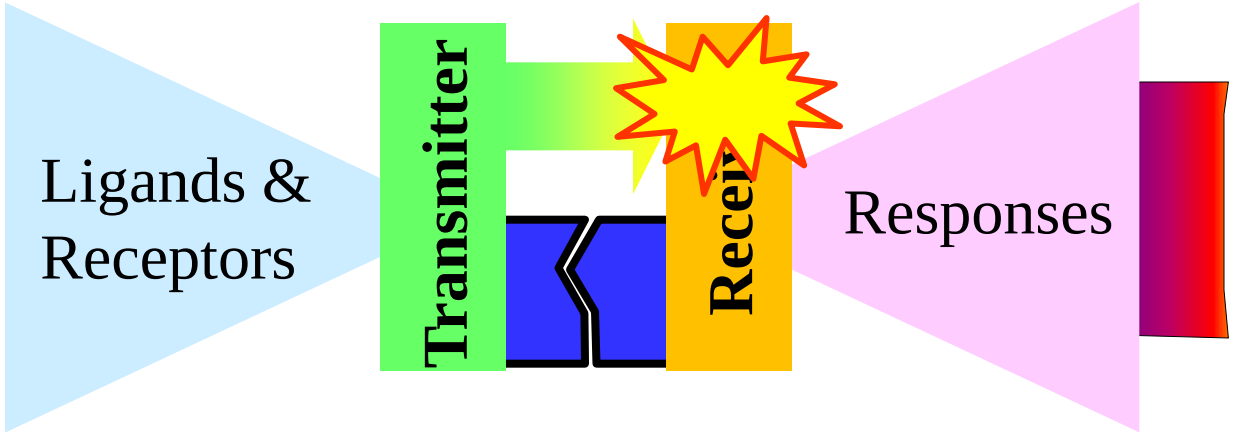
Shared
protocols

Note: Any wireless system and the Internet to which it is connected work the same way.

Flow of packets

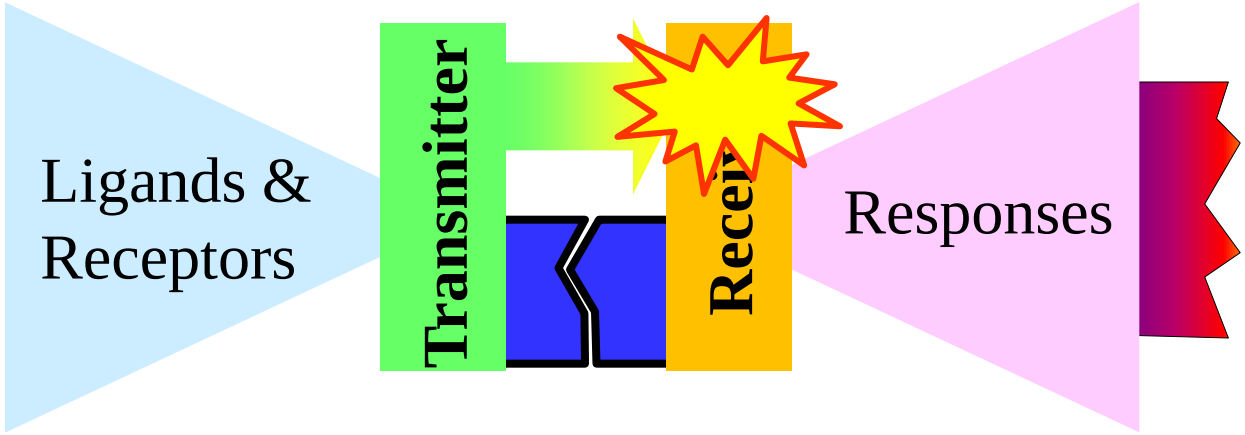


Recognition,
Specificity (MAC)



“Name” recognition
= molecular recognition
= localized functionally
= global spatially

Transcription factors
do “name” to “address”
translation



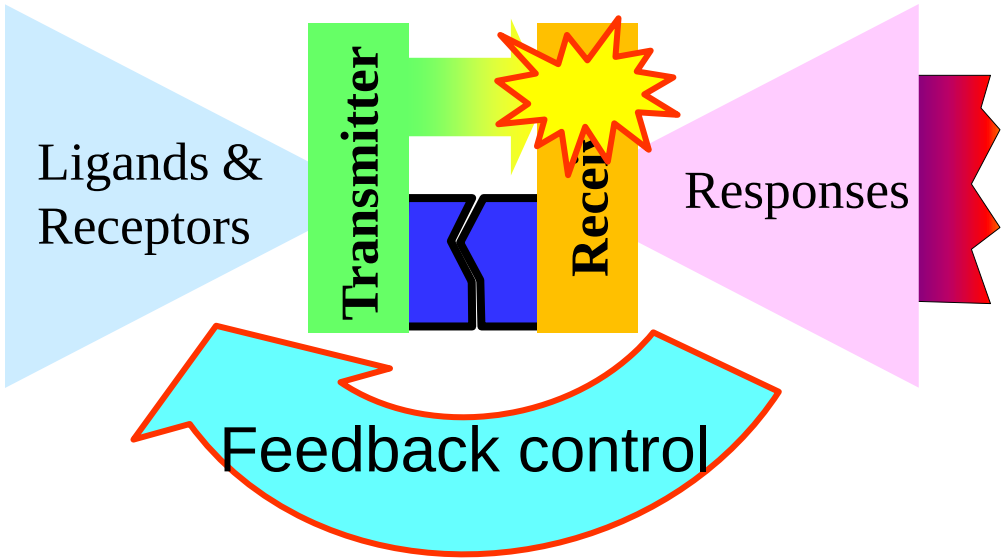
"Name" recognition
= molecular recognition
= localized functionally

Transcription factors
do "name" to "address"
translation

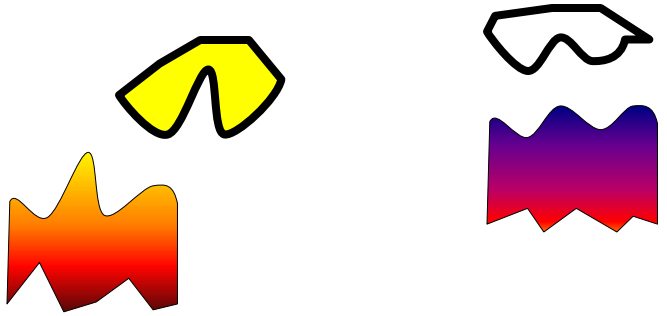
"Addressing"
= molecular recognition
= localized spatially

Both are
- Almost digital
- Highly programmable

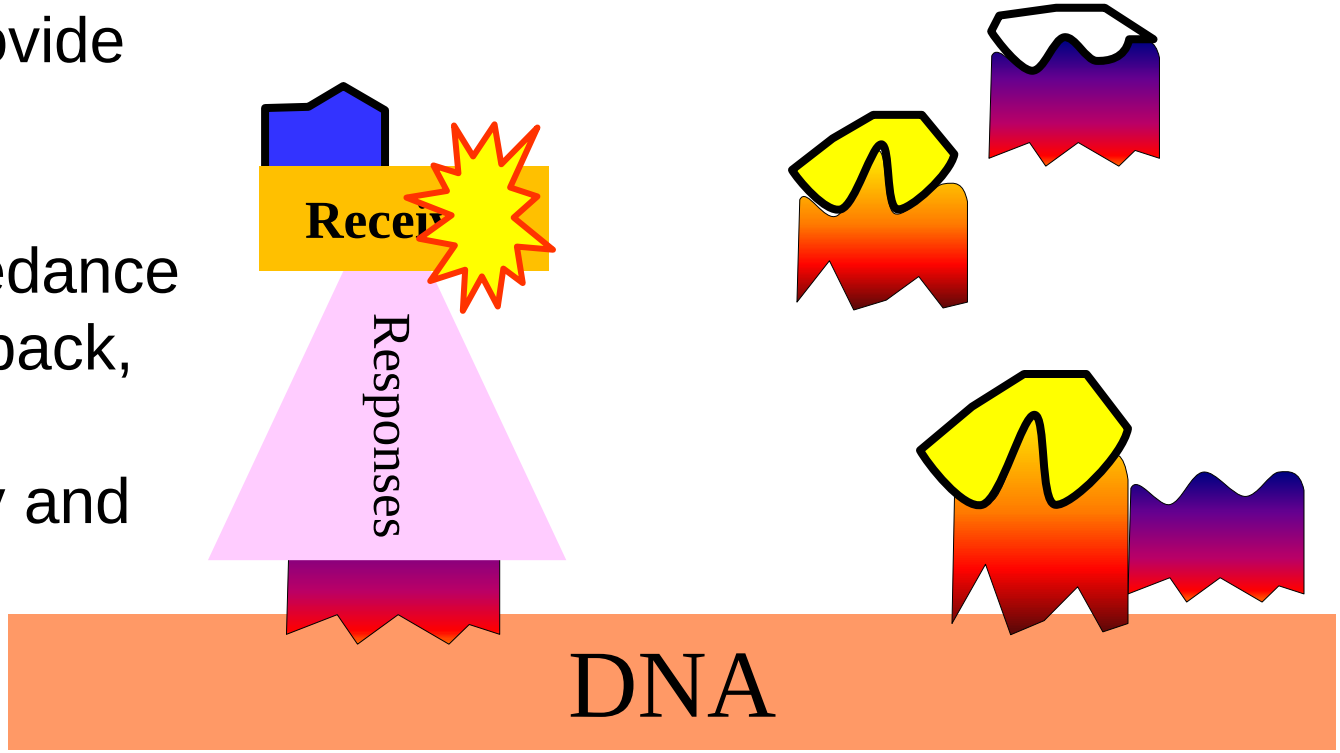
DNA



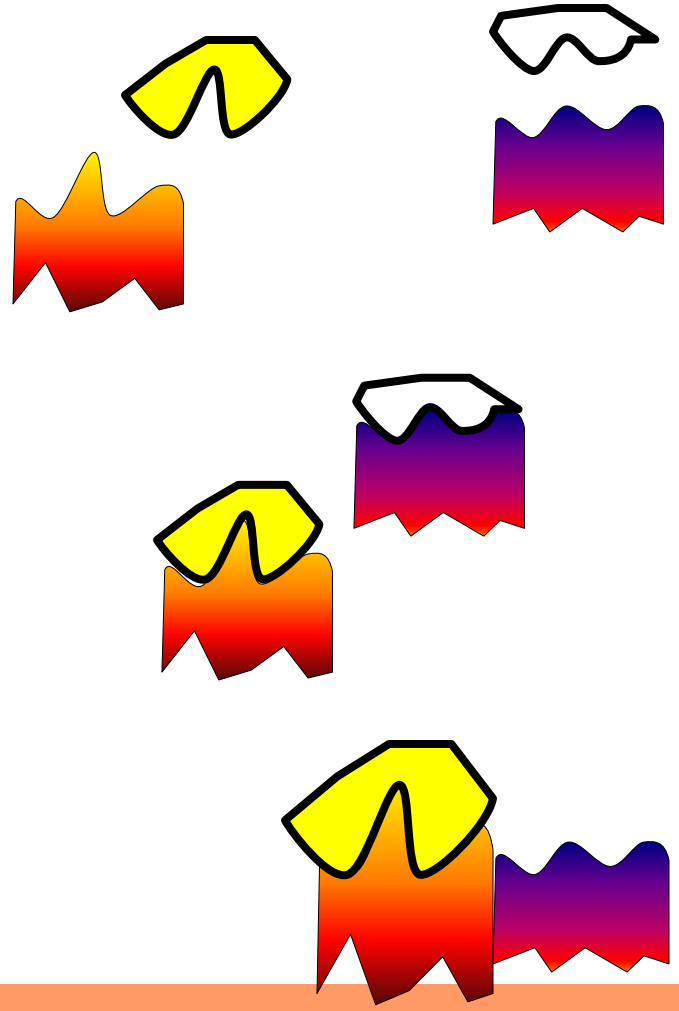
There are simpler transcription factors for sensing internal states



2CST systems provide speed, flexibility, external sensing, computation, impedance match, more feedback, but
greater complexity and overhead

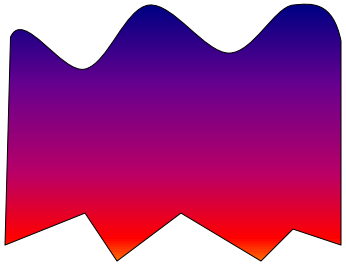


There are simpler transcription factors for sensing internal states



There are simpler transcription factors for sensing internal states

Sensor domains

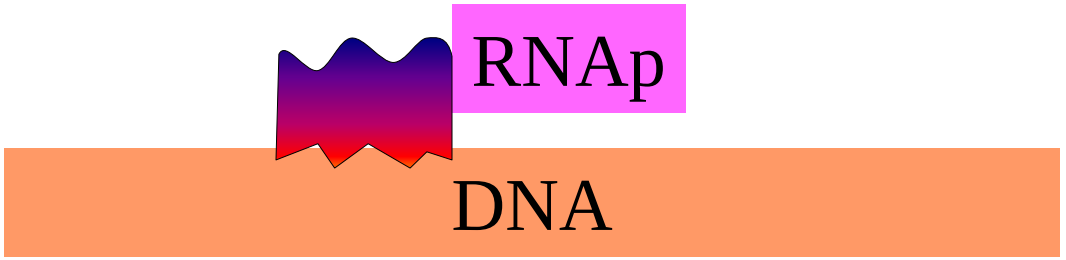


DNA and RNAp binding domains

Domains can be evolved independently or coordinated.

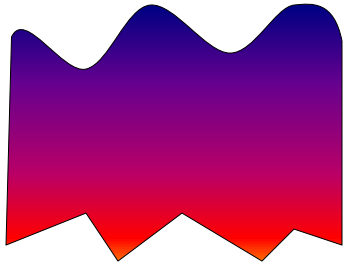
Application layer cannot access DNA directly.

Highly evolvable architecture.



This is like a “name to address” translation.

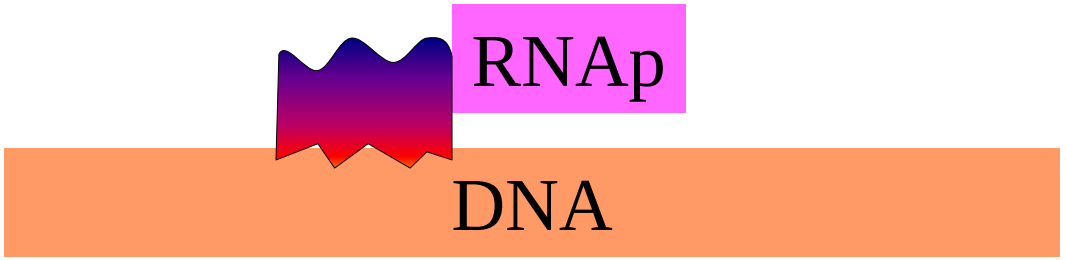
Sensor domains

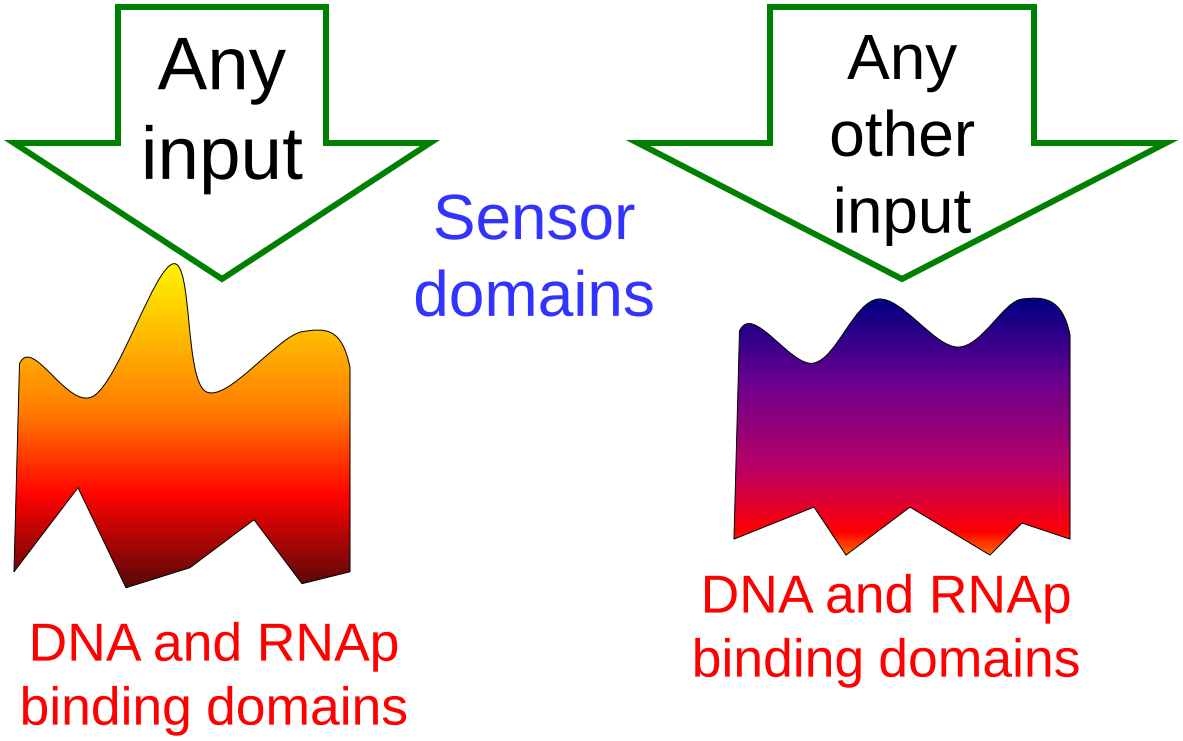


DNA and RNAp binding domains

Sensing the demand of the application layer

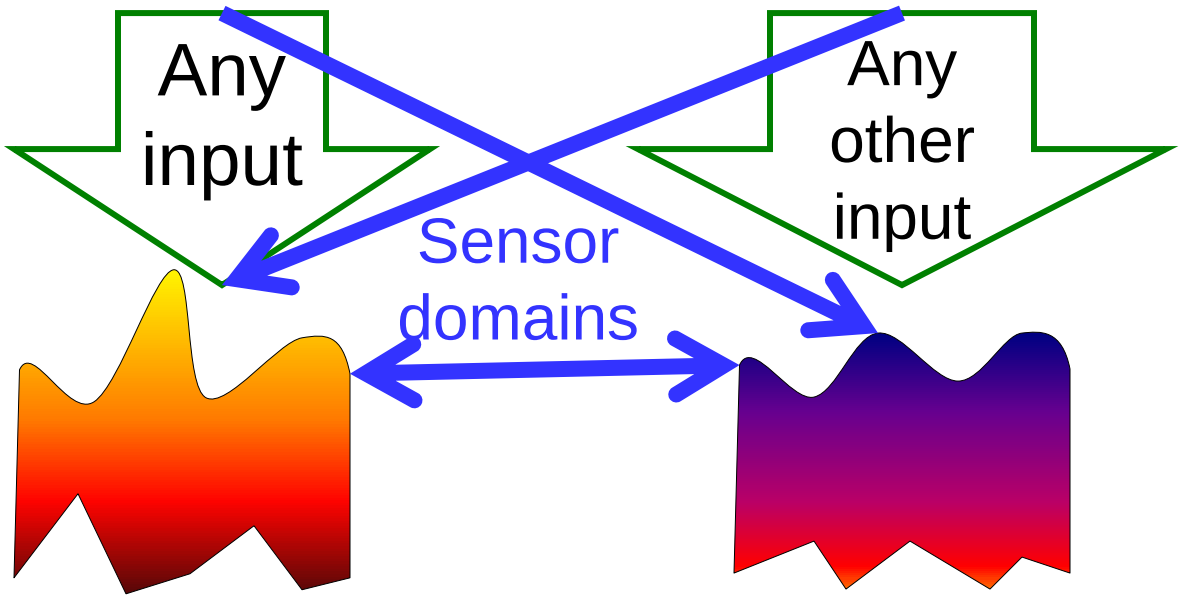
Initiating the change in supply





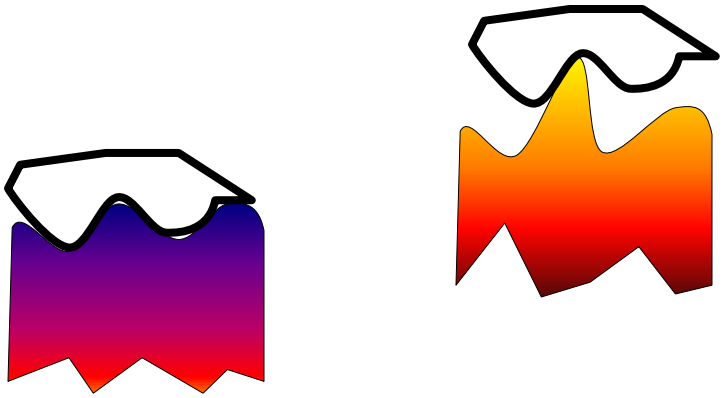
- Sensor sides attach to metabolites or other proteins
- This causes an allosteric (shape) change
- (Sensing is largely analog (# of bound proteins))
- Effecting the DNA/RNAp binding domains
- Protein and DNA/RNAp recognition is more digital
- Extensively discussed in both Ptashne and Alon

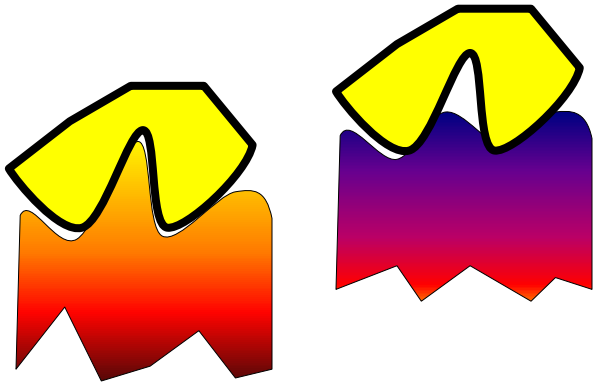
“Cross talk” can be finely controlled



- Application layer signals can be integrated or not
- Huge combinatorial space of (mis)matching shapes
- A functionally meaningful “name space”
- Highly adaptable architecture
- Interactions are fast (but expensive)
- Return to this issue in “signal transduction”

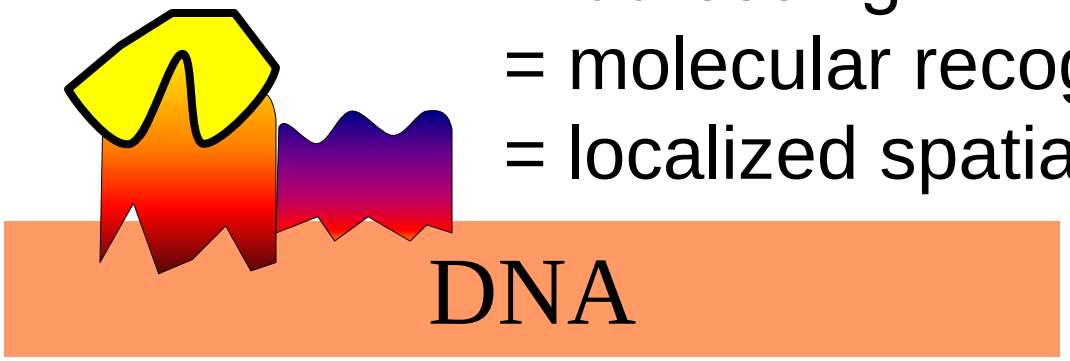
“Name” recognition
= molecular recognition
= localized functionally
= global spatially





Transcription factors
do “name” to “address”
translation

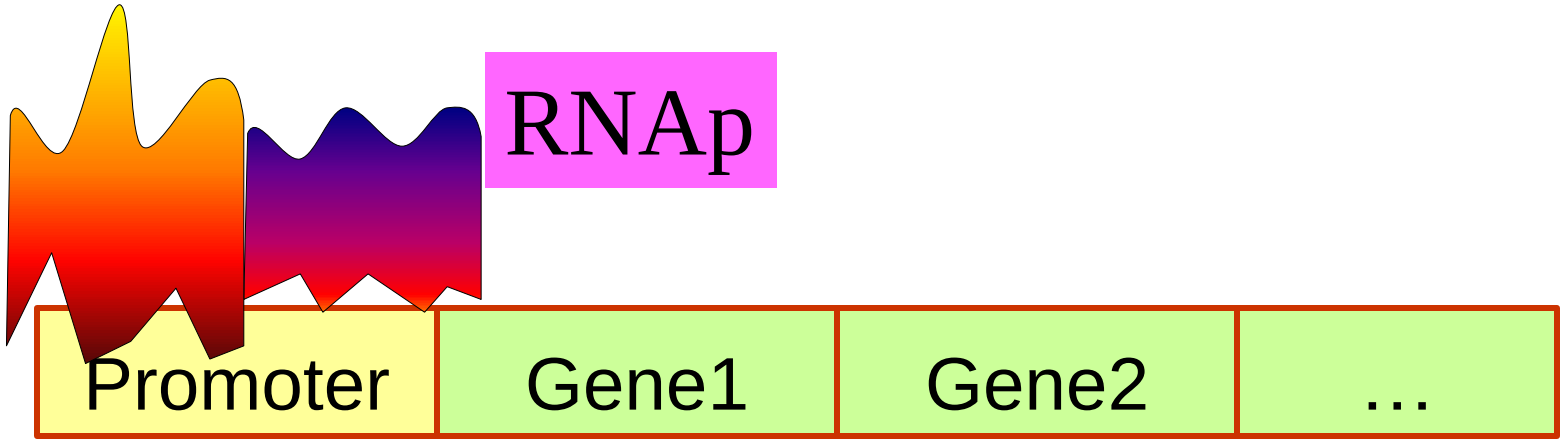
Both are
• Almost digital
• Highly programmable



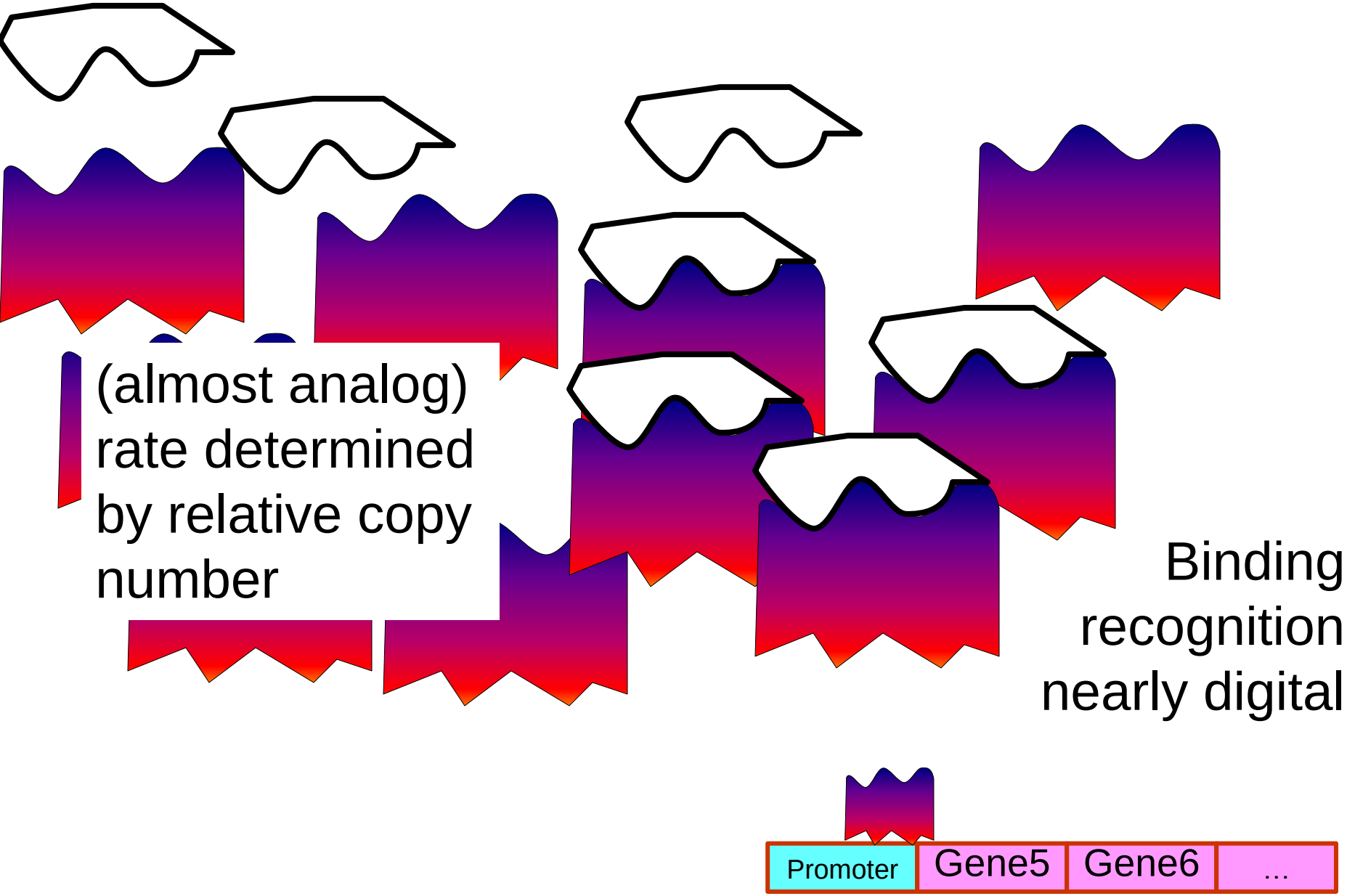
“Addressing”
= molecular recognition
= localized spatially

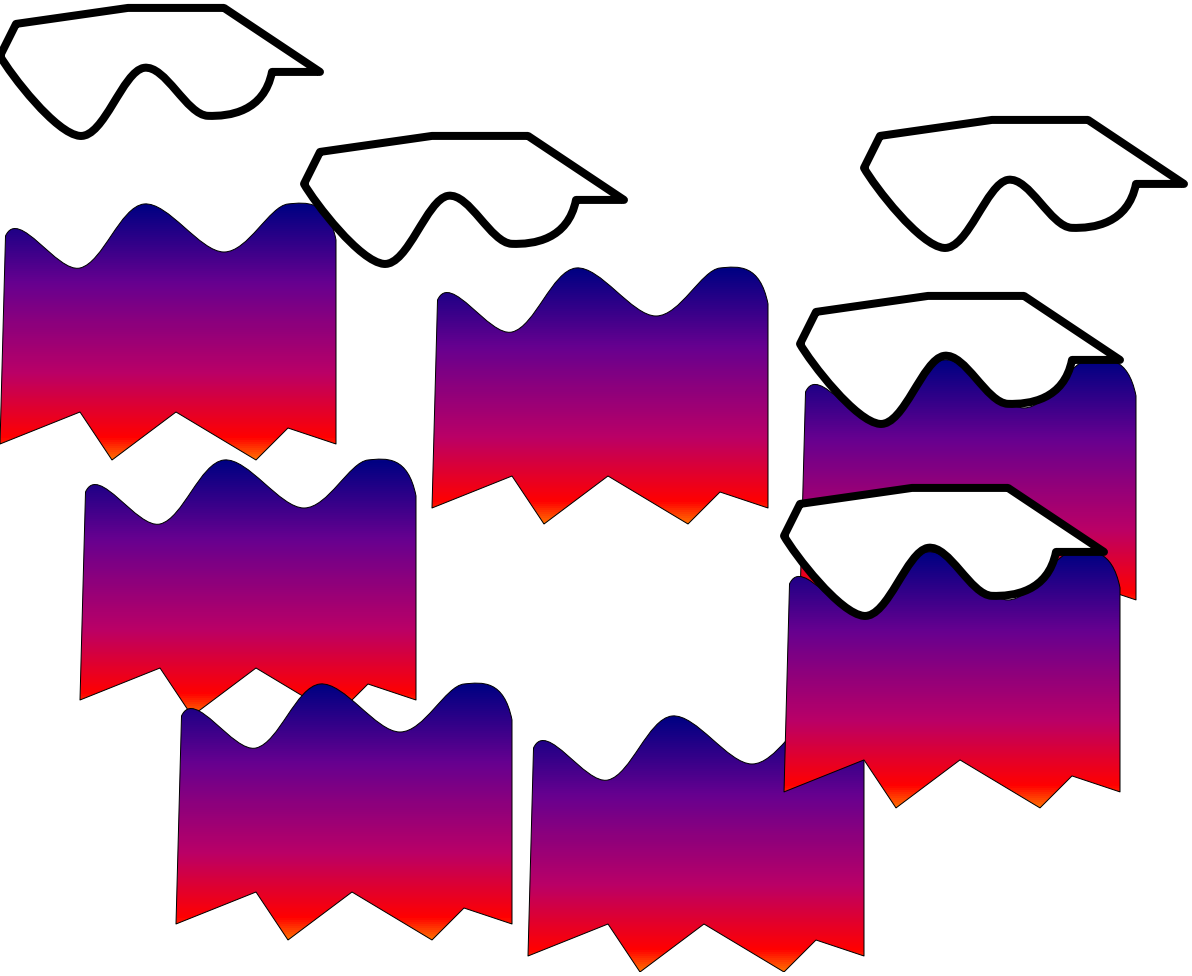
Can activate or repress

And work in complex logical combinations



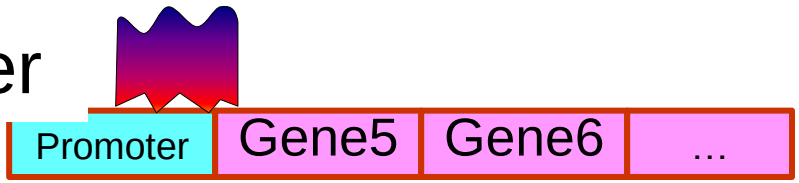
- Both protein and DNA sides have sequence/shape
- Huge combinatorial space of “addresses”
- Modest amount of “logic” can be done at promoter
- Transcription is very noise (but efficient)
- Extremely adaptable architecture

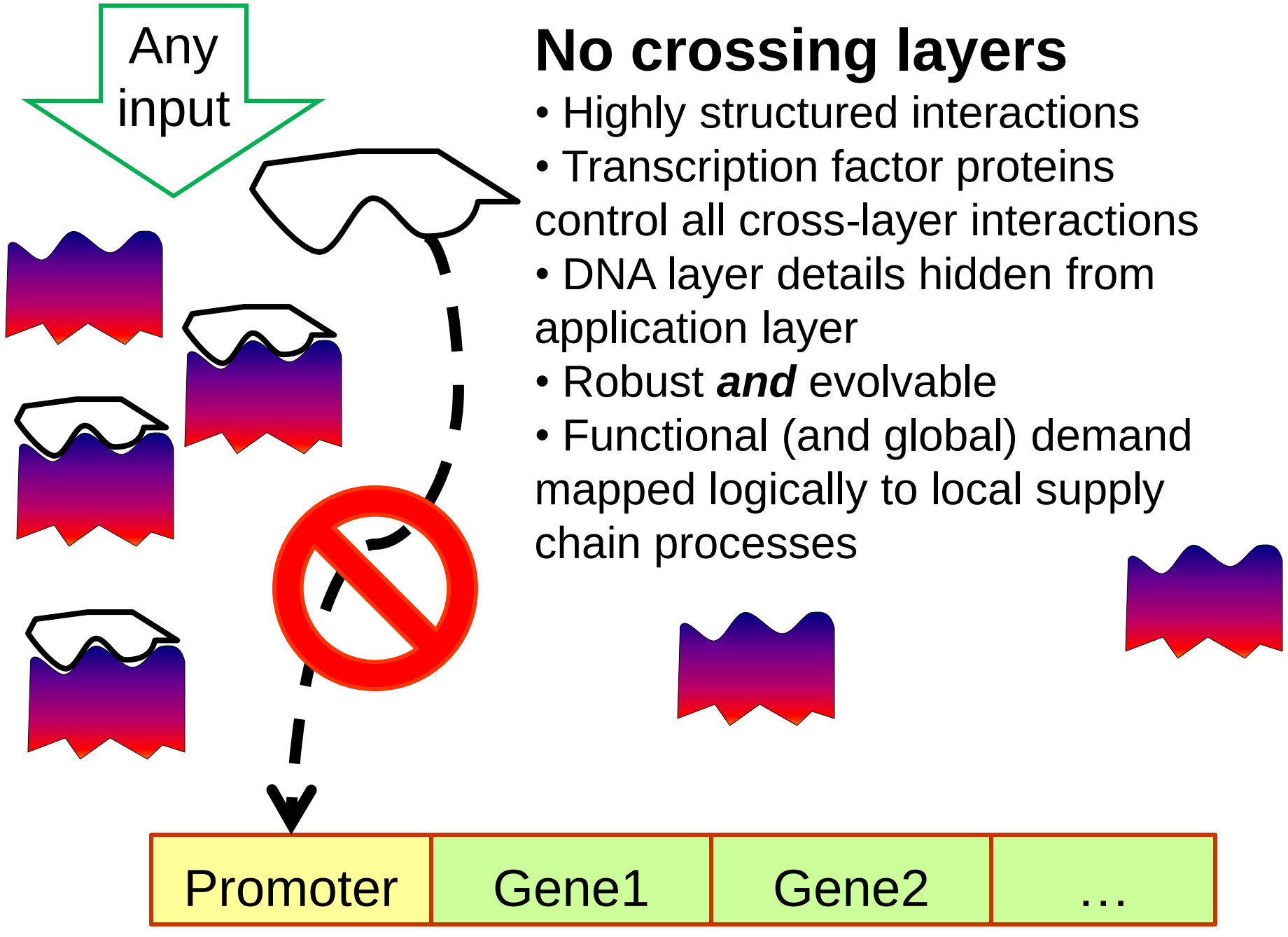

(almost analog)
rate determined
by relative copy
number
Binding
recognition
nearly digital
Promoter
Gene5
Gene6
…



rate (almost analog)
determined by copy number

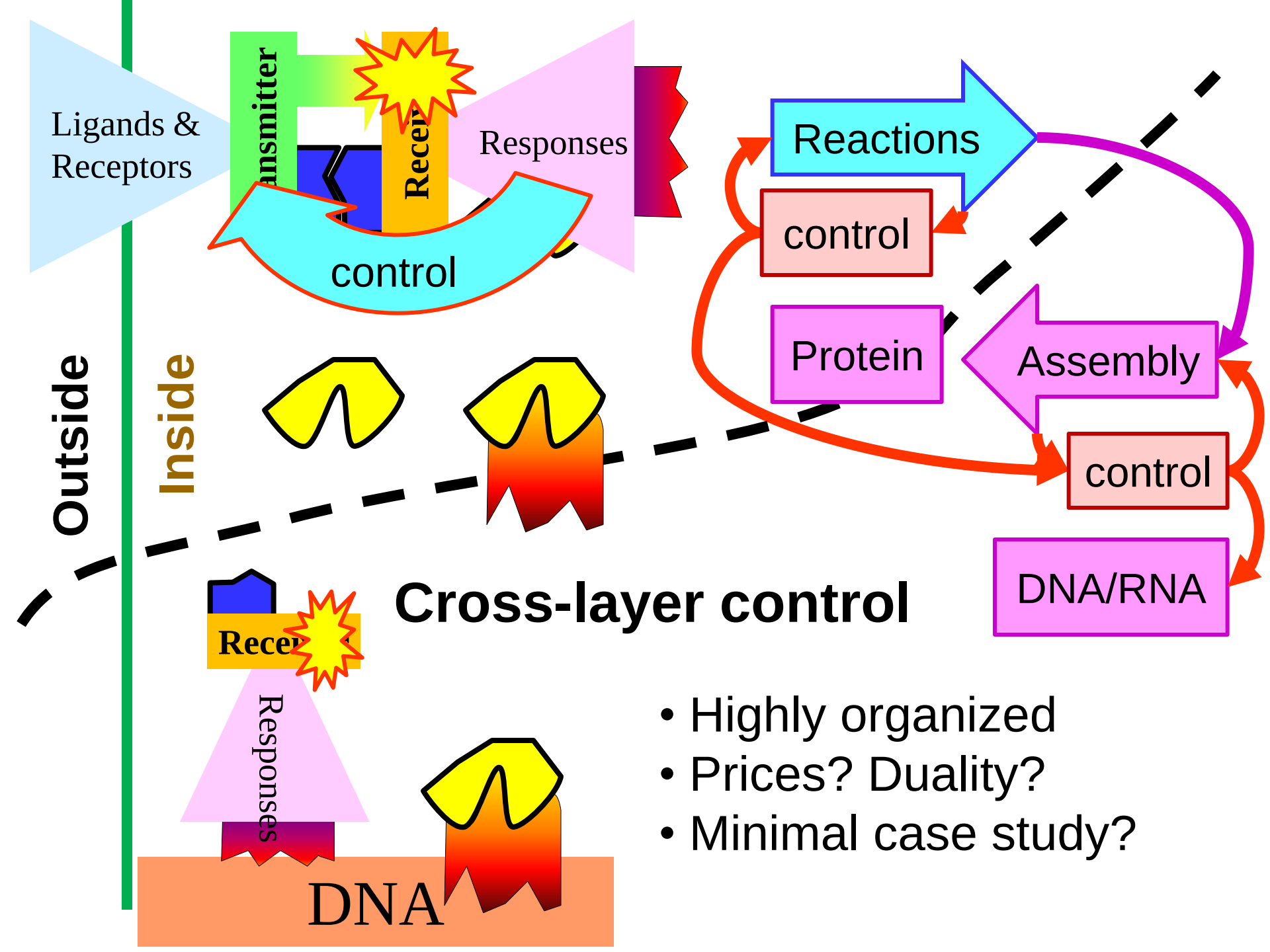
Recall: can work by pulse code modulation so for small copy number does digital to analog conversion





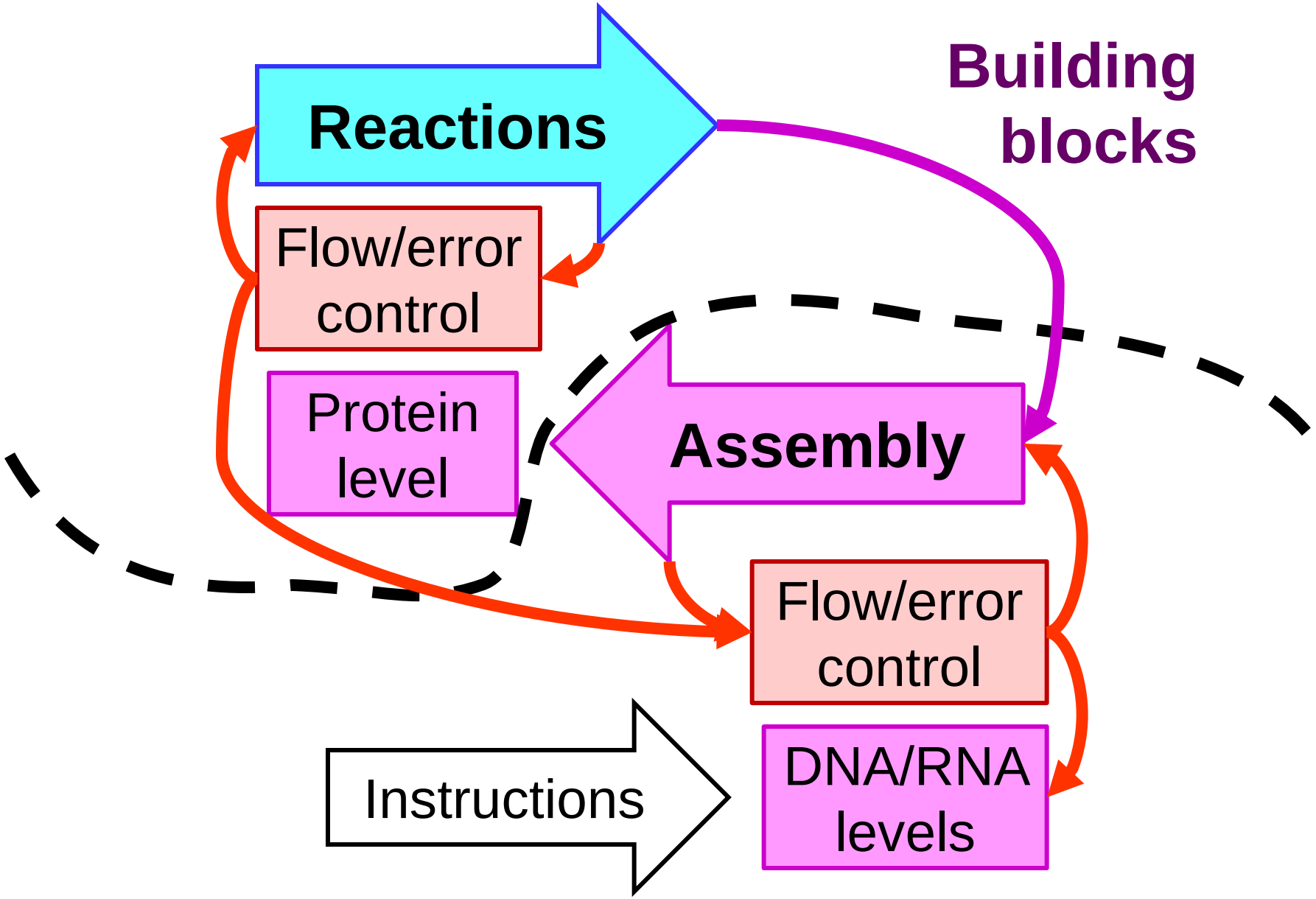
No crossing layers

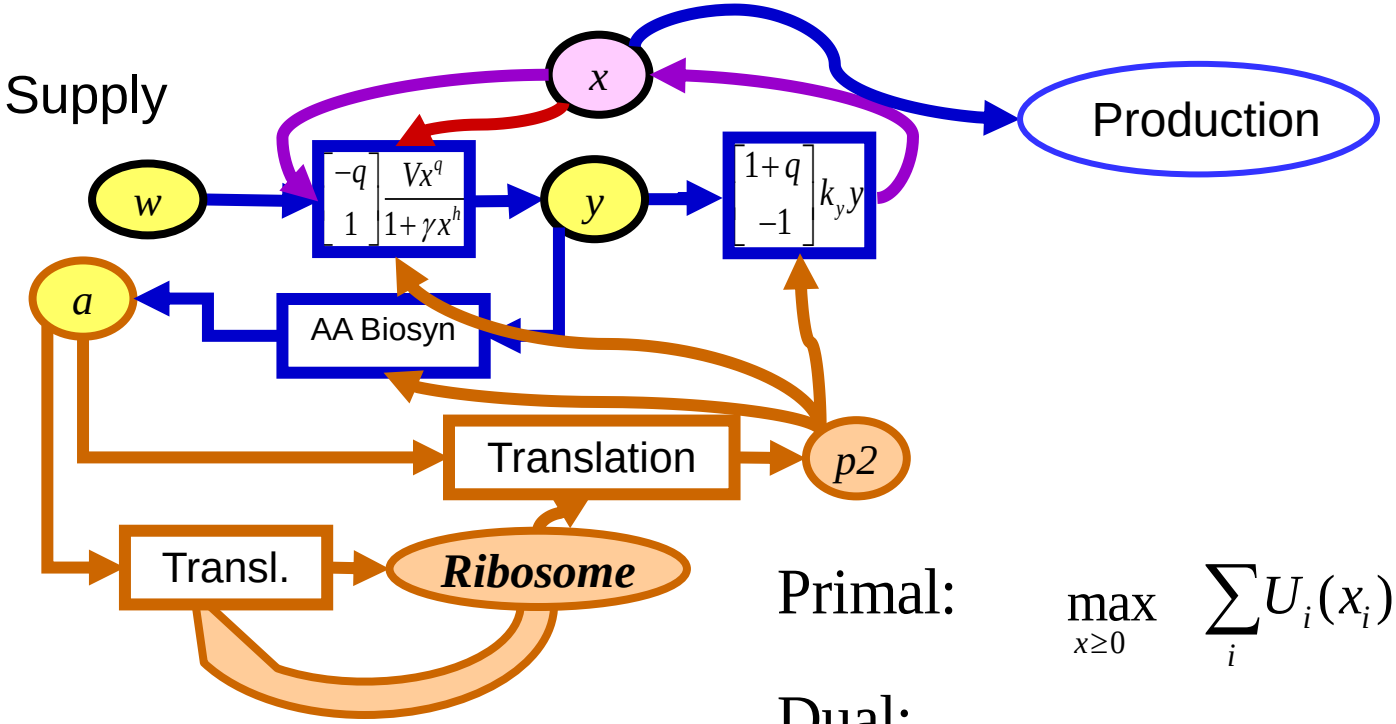
- Highly structured interactions
- Transcription factor proteins control all cross-layer interactions
- DNA layer details hidden from application layer
- Robust ***and*** evolvable
- Functional (and global) demand mapped logically to local supply chain processes



Cross-layer control

- Highly organized
- Prices? Duality?
- Minimal case study?


Reactions
Building blocks
Flow/error control
Protein level
Assembly
Flow/error control
Instructions
DNA/RNA levels



No duality gaps?
Multipath routing?
Coherent pricing?

Primal: $\max_{x \geq 0} \sum_i U_i(x_i)$ subject to $Rx \leq c$

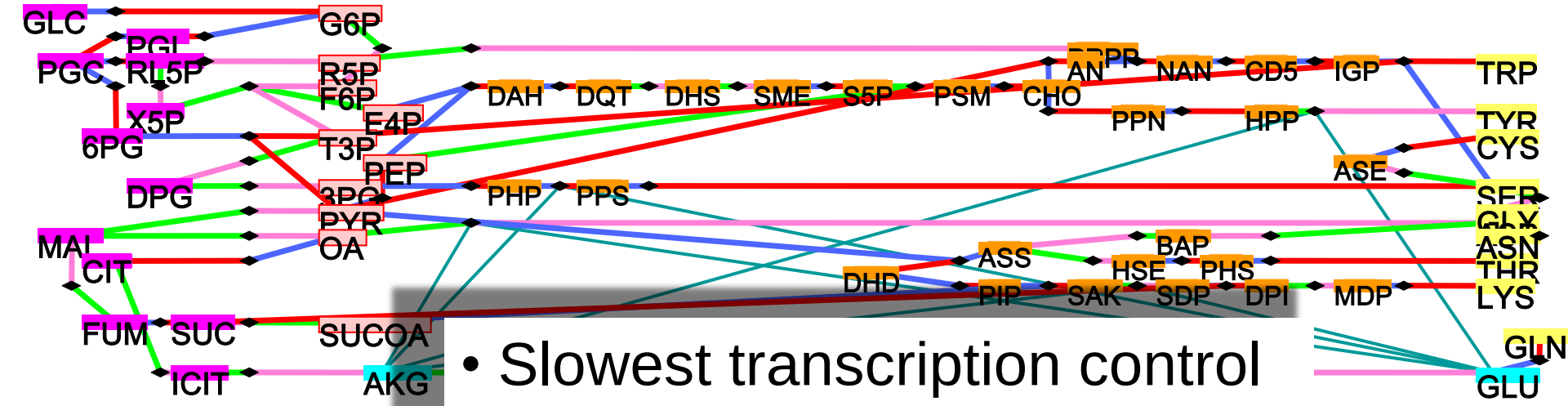
Dual:

$$\min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - \sum_l p_l \left(R_{li} x_i - c_l \right) \right) \right)$$

$$= \min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - x_i \sum_l R_{li} p_l \right) + \sum_l p_l c_l \right)$$

$$= \min_{p \geq 0} \left(\sum_i \max_{x_i \geq 0} \left(U_i(x_i) - x_i q_i \right) + \sum_l p_l c_l \right)$$

$$\Rightarrow U_i'(x_i) = q_i \Rightarrow x_i = \left(U_i' \right)^{-1} (q_i)$$



- Slowest transcription control
- Complex transcription factors
- Lowest metabolic overhead
- Easily reprogrammed

Any input

RNA

Transc.

mRNA

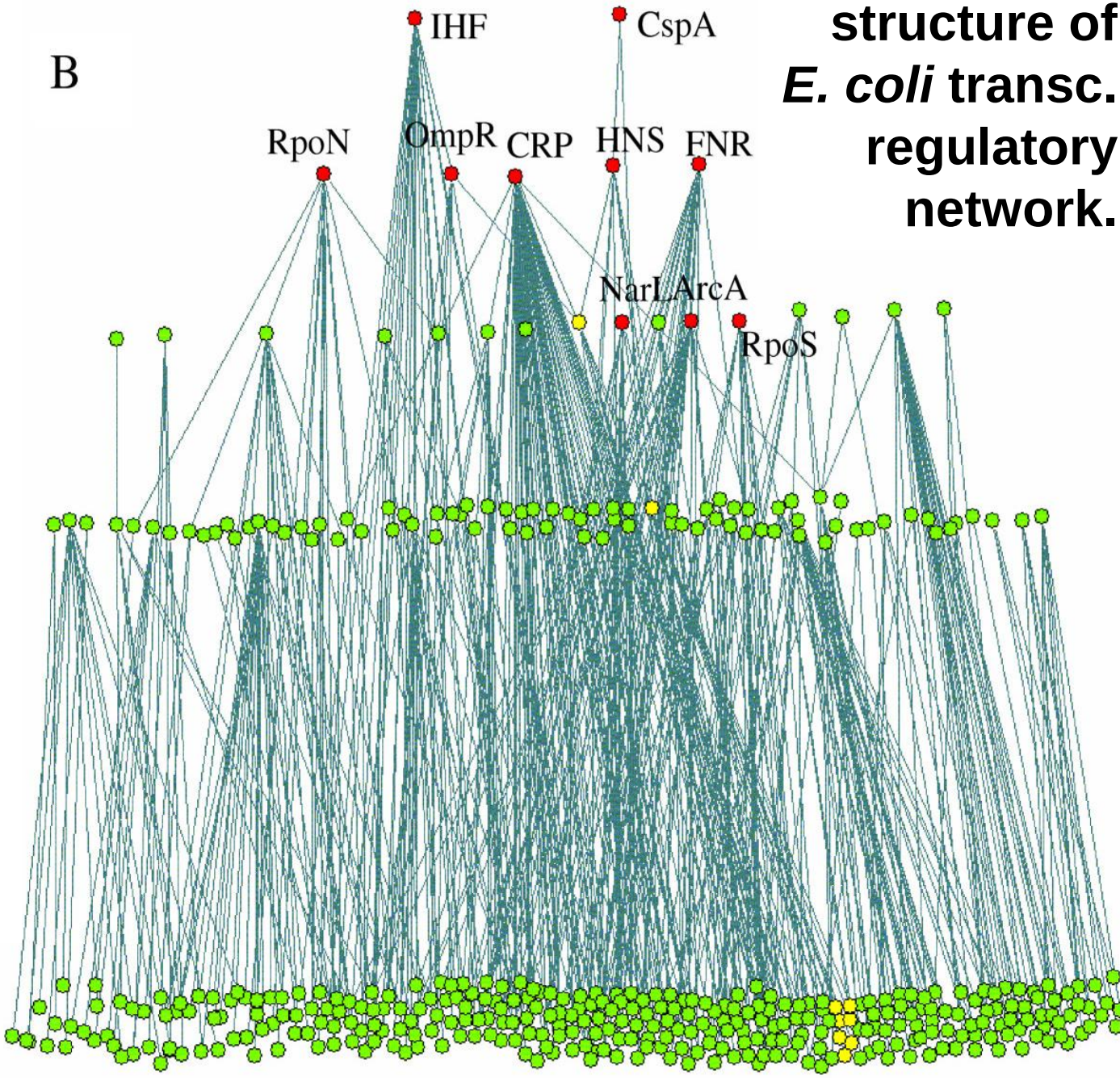
RNAp

Gene

Hierarchical structure of *E. coli* transc. regulatory network.

All transcriptional regulatory links are downward. Nodes are operons. Global regulators are red. Yellow marked nodes are operons in the longest regulatory pathway related with flagella motility.

Ma *et al. BMC Bioinformatics* 2004 **5**:199 doi:10.1186/1471-2105-5-199



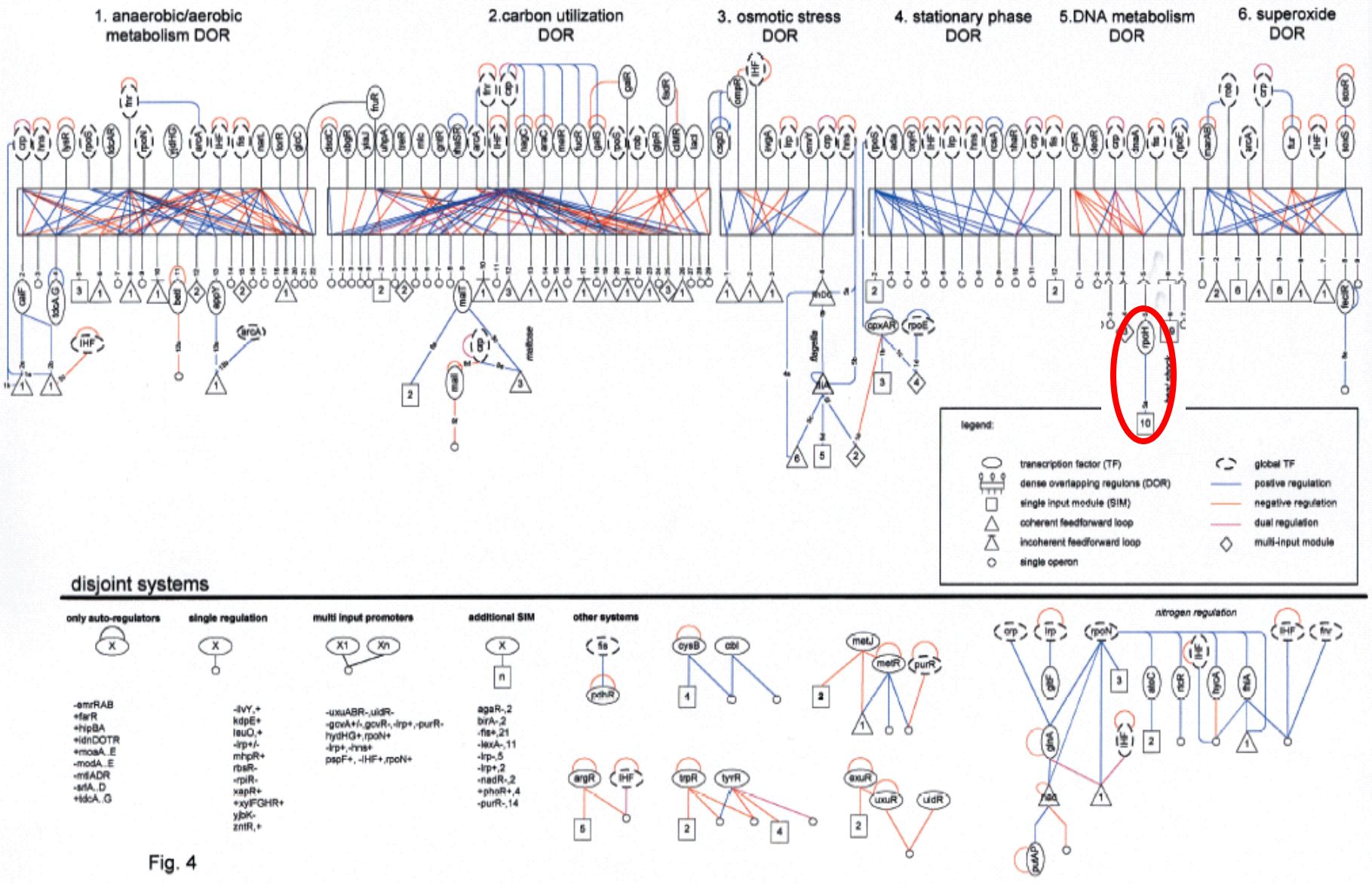
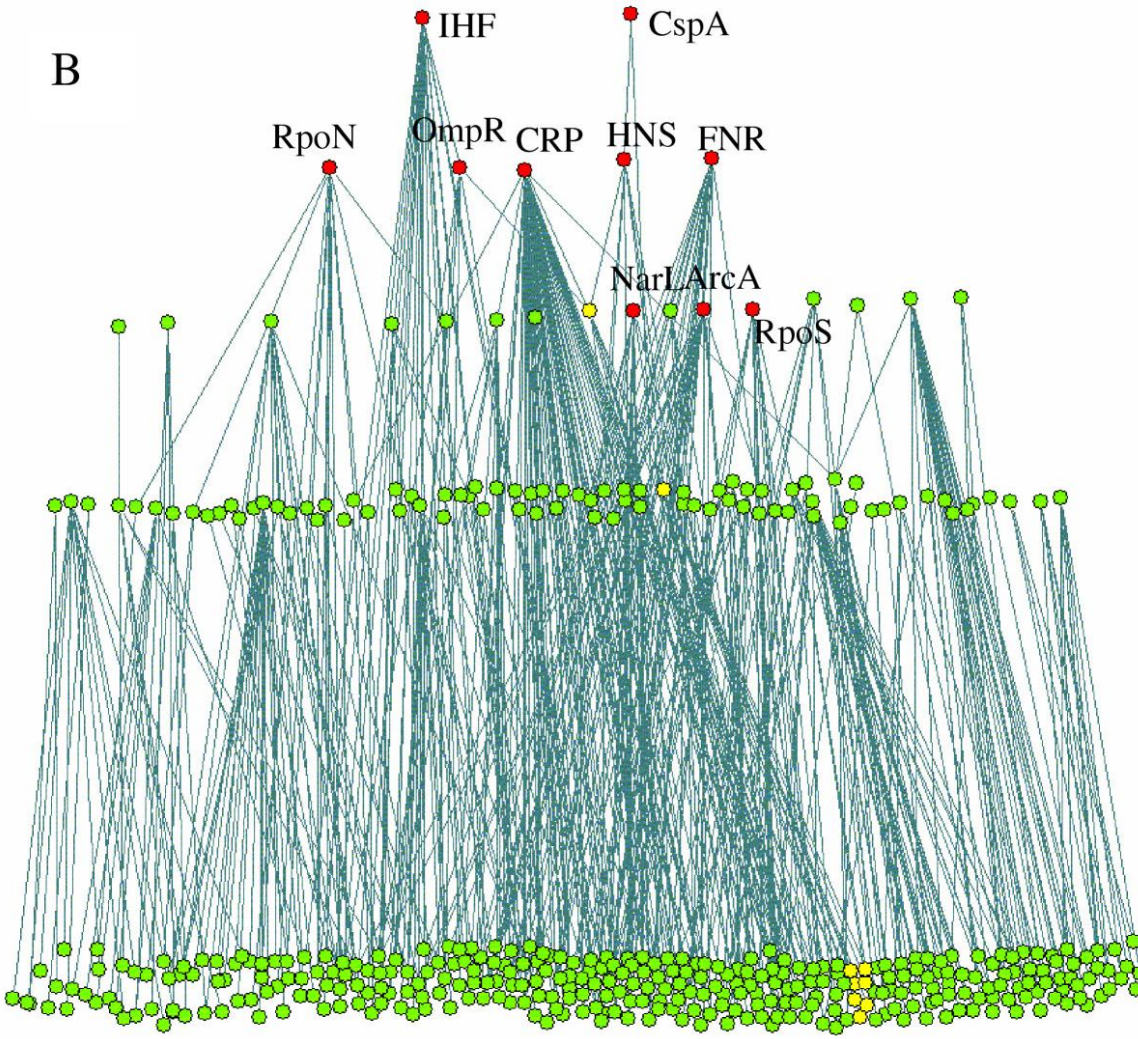

1. anaerobic/aerobic metabolism DOR
2.carbon utilization DOR
3. osmotic stress DOR
4. stationary phase DOR
5.DNA metabolism DOR
6. superoxide DOR
legend:
transcription factor (TF)
dense overlapping regulons (DOR)
single input module (SIM)
coherent feedforward loop
incoherent feedforward loop
single operon
global TF
positive regulation
negative regulation
dual regulation
multi-input module
disjoint systems
only auto-regulators
single regulation
multi input promoters
additional SIM
other systems
-emrRAB
+fsrR
+hipBA
+idnDOTR
+mosA..E
-modA..E
-mtlADR
-srlA..D
+tdcA..G
-ilvY,+
kdpE+
lsuO,+
-lrp+/-
mhpR+
rbsR-
-rplR-
xapR+
+xylFGHR+
yjbK-
zntR,+
-uxuABR-,uidR-
-gcvA+/-,gcvR-,-lrp+,-purR-
hydHG+,rpoN+
-lrp+,-hns+
pspF+, -IHF+,rpoN+
agaR-,2
birA-,2
-fis+,21
-lexA-,11
-lrp-,5
-lrp+,2
-nadR-,2
+phoR+,4
-purR-,14
nitrogen regulation

Fig. 4

Note: all feedback in this picture has been removed in two ways:

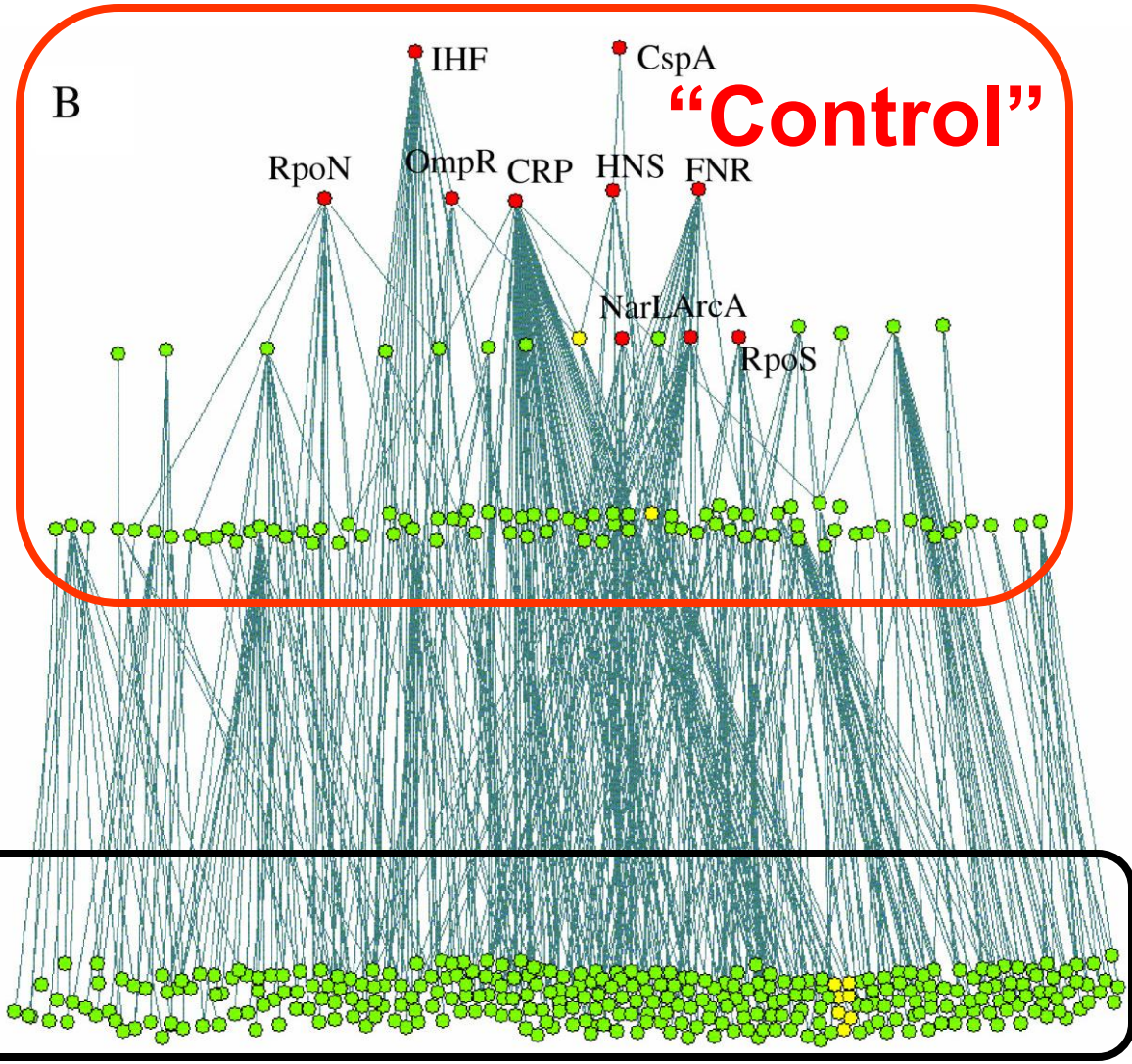
1) There are self-loops where an operon is controlled by one it's own genes
2) All the real complex control is in the protein interactions not shown (e.g. see heat shock details)

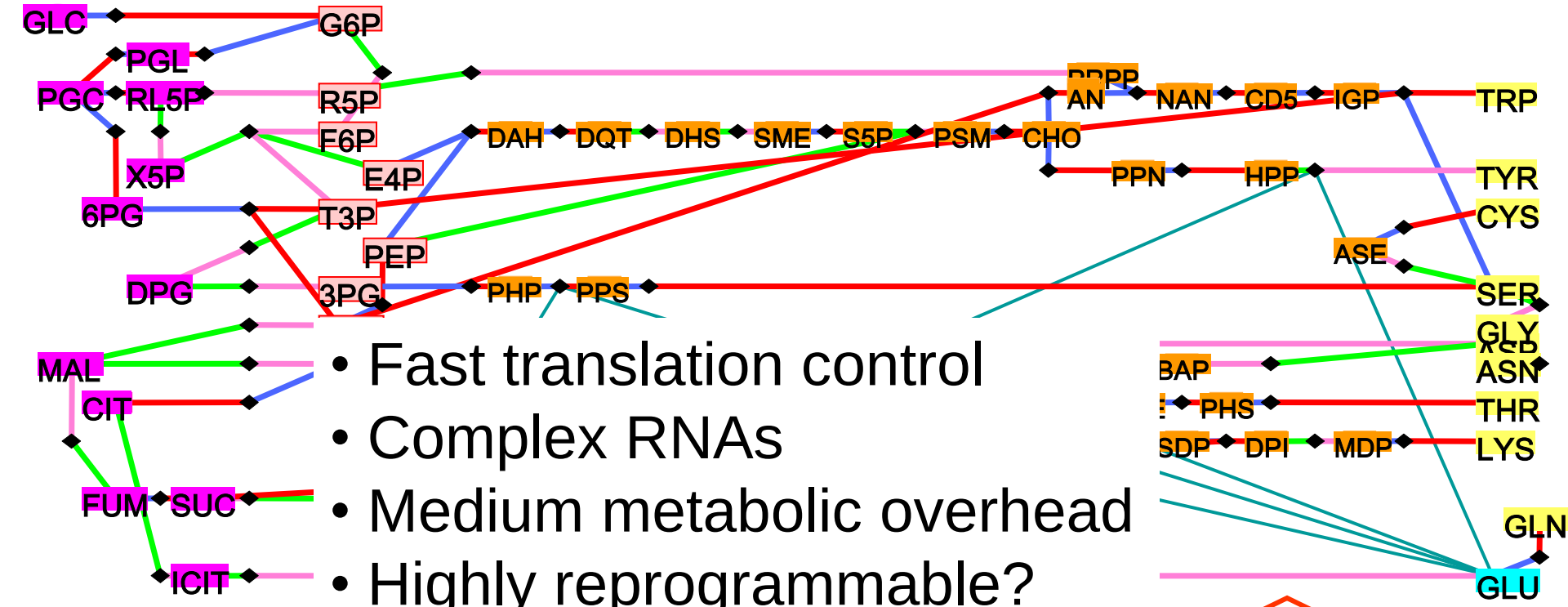
These are not really ***control*** systems, they just initiate manufacturing



This architecture has limited scalability:

1) Fast diffusion can only work in small volumes
2) The number of proteins required for control grows superlinearly with the number of enzymes (Mattick)





- Fast translation control
- Complex RNAs
- Medium metabolic overhead
- Highly reprogrammable?

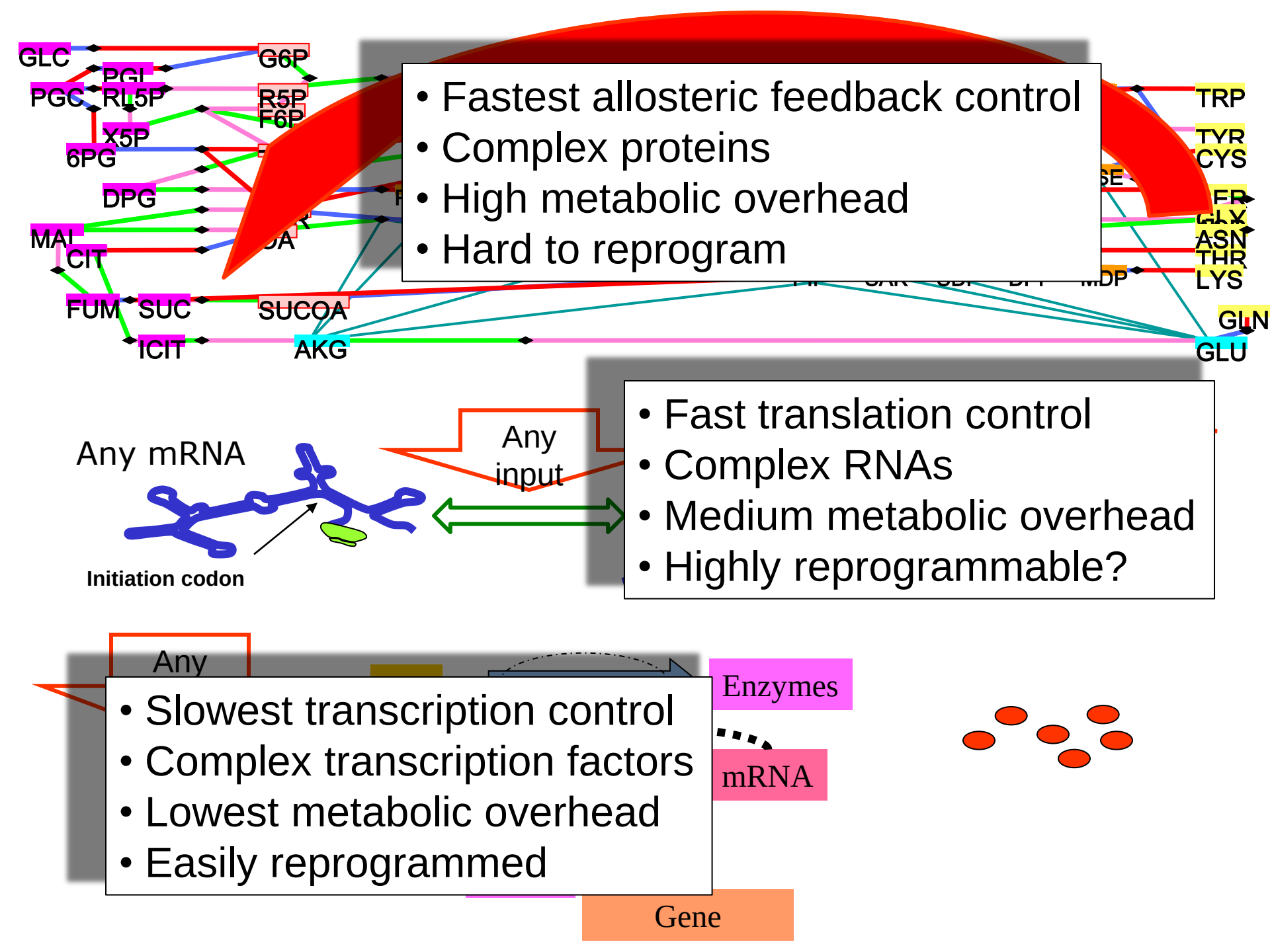
Any mRNA

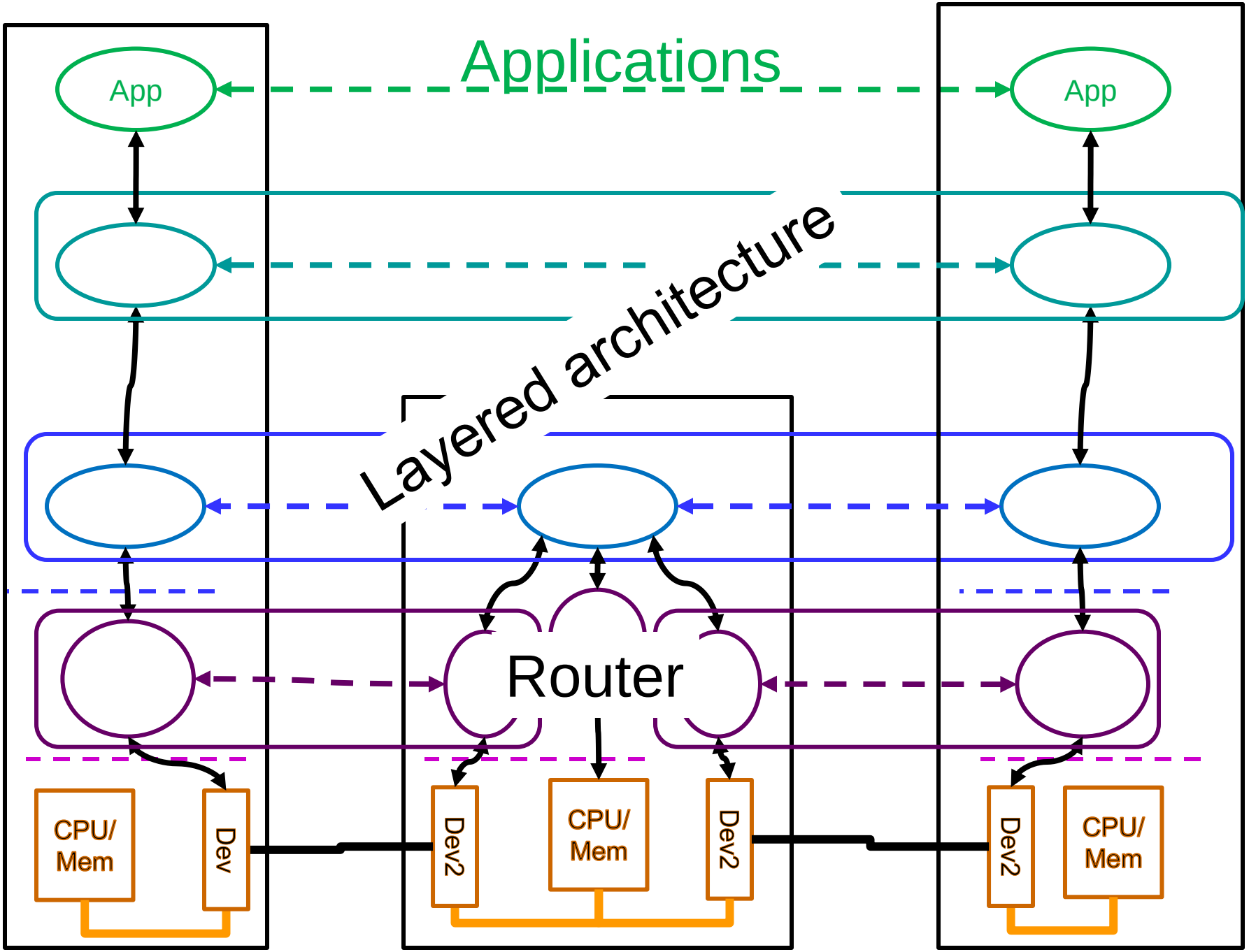
Any input

Any protein

Translation

Initiation codon

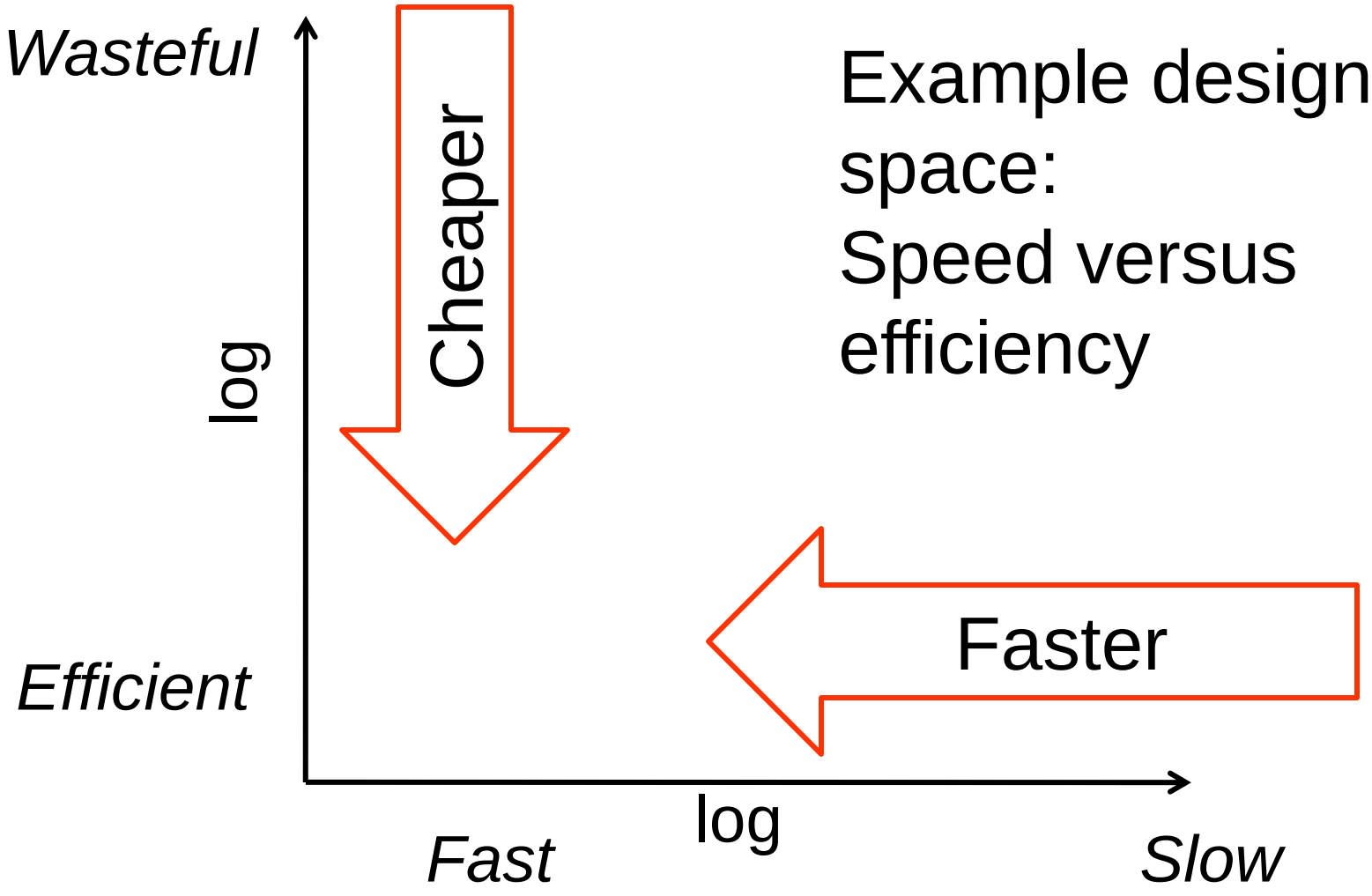

GLC
G6P
PGI
PGC
RL5P
R5P
F6P
X5P
6PG
DPG
MAL
CIT
FUM
SUC
SUCOA
ICIT
AKG
TRP
TYR
CYS
ASN
THR
LYS
GLN
GLU
• Fastest allosteric feedback control
• Complex proteins
• High metabolic overhead
• Hard to reprogram
Any mRNA
Initiation codon
Any input
• Fast translation control
• Complex RNAs
• Medium metabolic overhead
• Highly reprogrammable?
Any
• Slowest transcription control
• Complex transcription factors
• Lowest metabolic overhead
• Easily reprogrammed
Enzymes
mRNA
Gene


Applications
App
App
Layered architecture
Router
CPU/
Mem
Dev
Dev2
CPU/
Mem
Dev2
Dev2
CPU/
Mem

Clean slate layering?

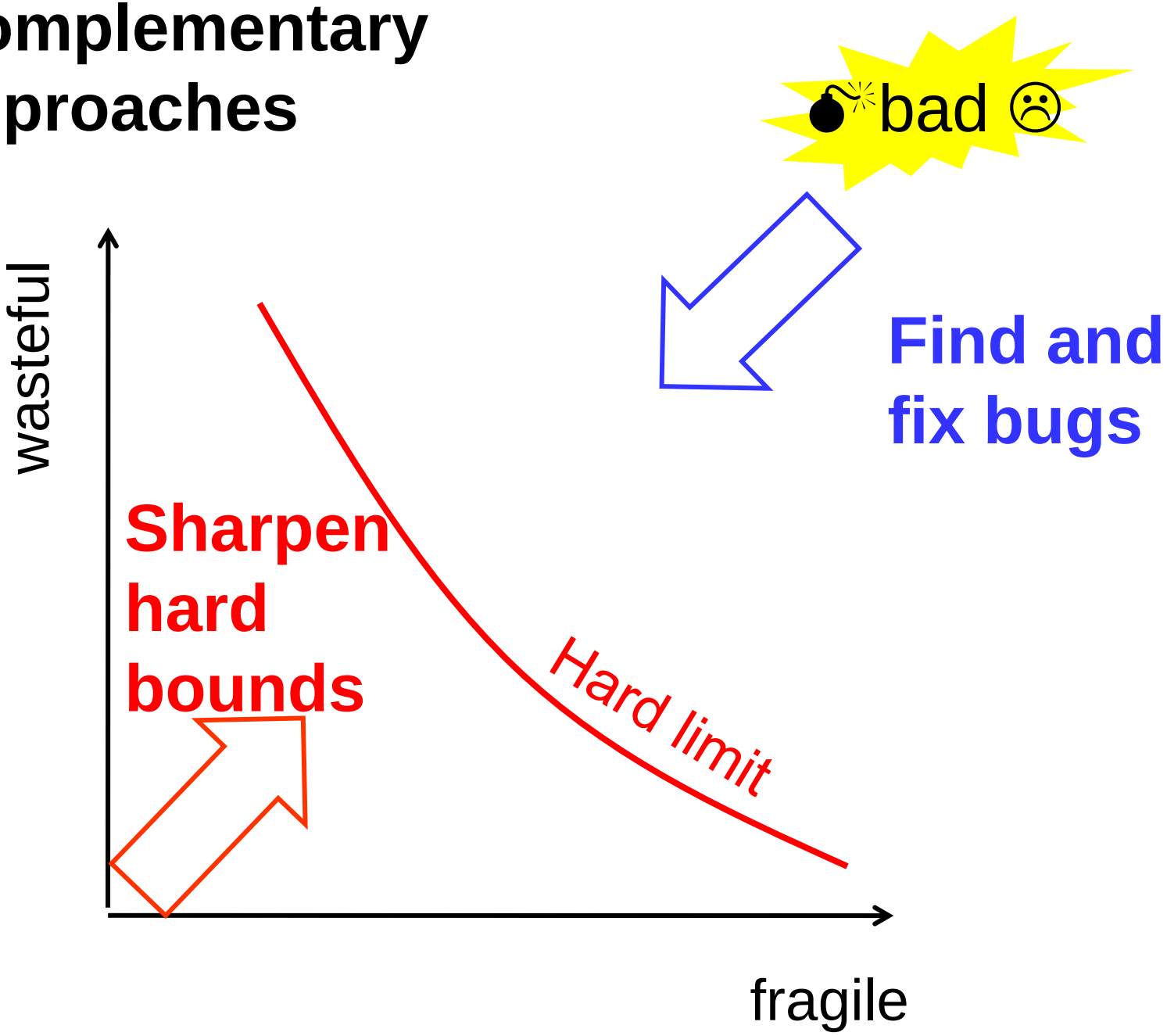
- Two “macrolayers” with a new, higher “waist”
  - Upper: Managing content, function, naming
  - Lower: Managing physical resources, addressing
- Lower layers: map to physical addresses (PNA)
  - Recursive “microlayers” of control and management
  - Different scopes (more global and lumped to more local and detailed)
  - No global addresses, hide details, addresses
- Cleaner role of optimization and control?
- Integration with naming and addressing
- Align robustness and security

Design tradeoffs



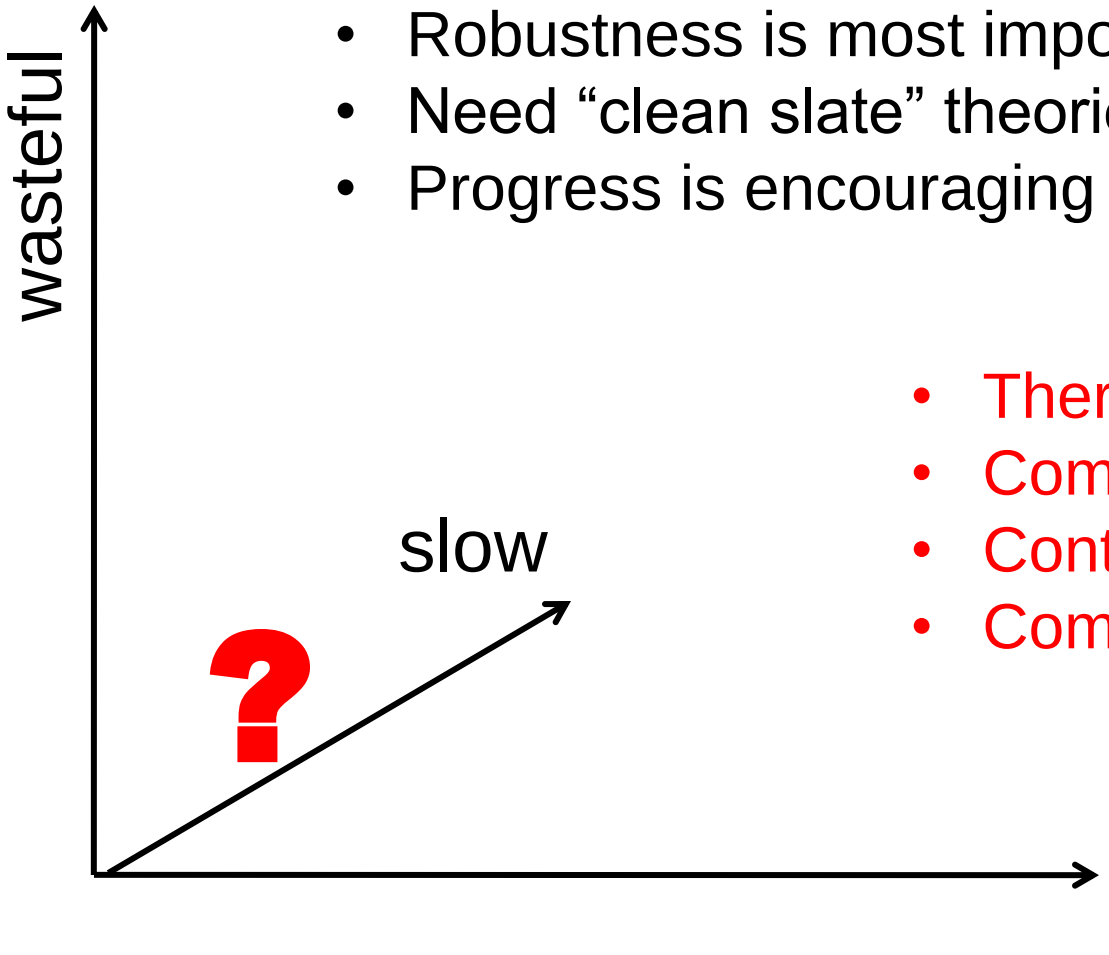
Example design space:
Speed versus efficiency

Complementary approaches



Standard theories are severely limited

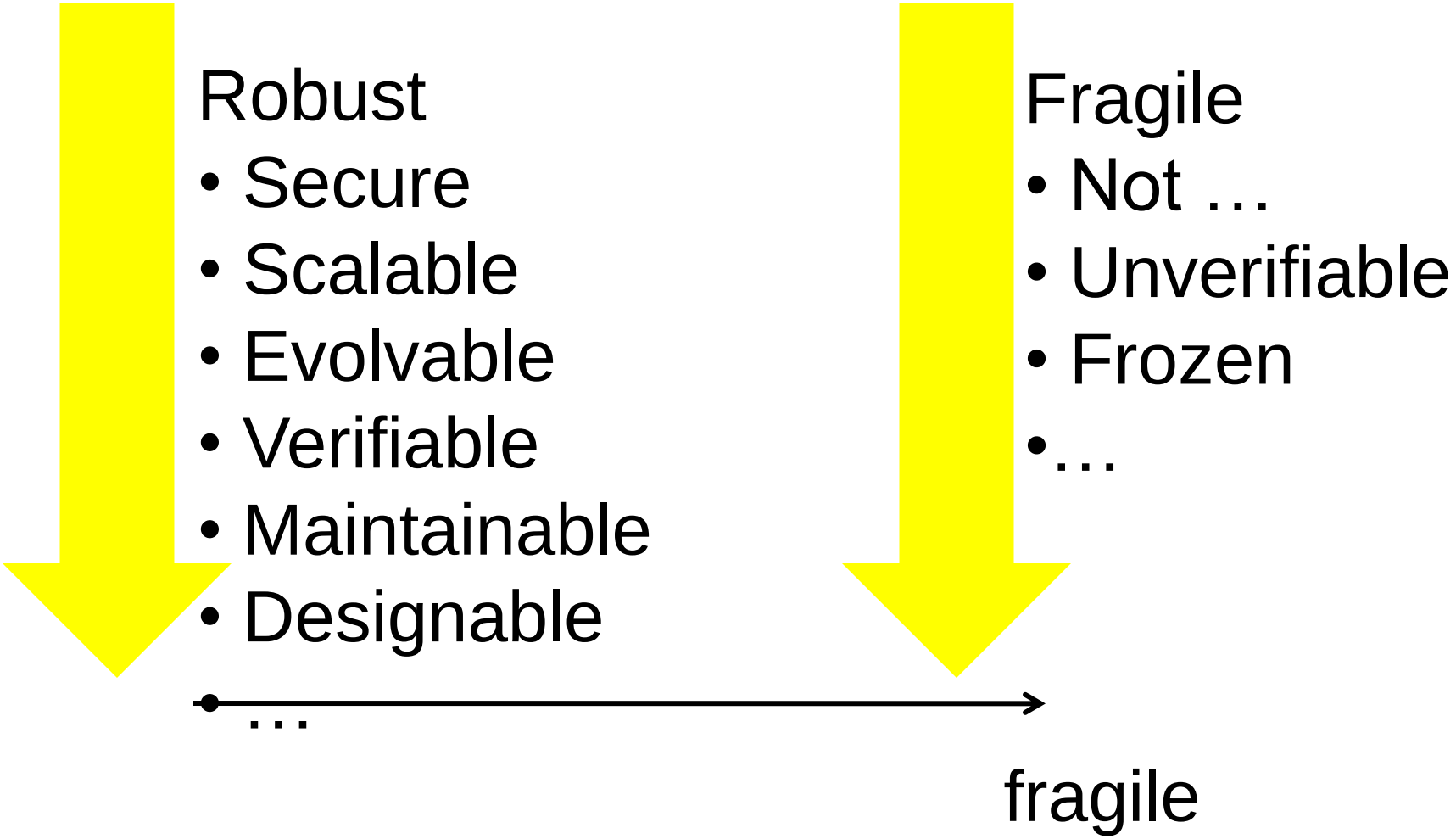
- Each focuses on few dimensions
- Important tradeoffs are ***across*** these dimensions
- Speed vs efficiency vs robustness vs …
- Robustness is most important for complexity
- Need “clean slate” theories
- Progress is encouraging



- Thermodynamics (Carnot)
- Communications (Shannon)
- Control (Bode)
- Computation (Turing)

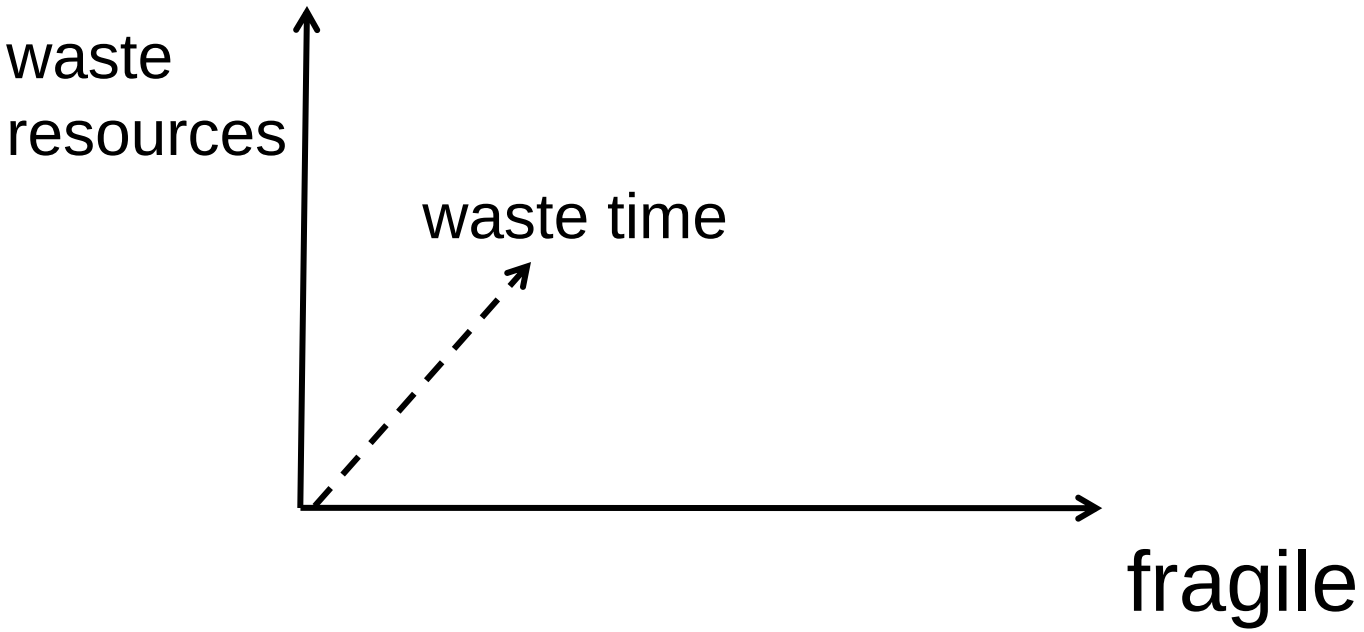
Most dimensions are robustness

Collapse for visualization



- Important tradeoffs are ***across*** these dimensions
- Speed vs efficiency vs robustness vs …
- Robustness is most important for complexity
- Collapse efficiency dimensions

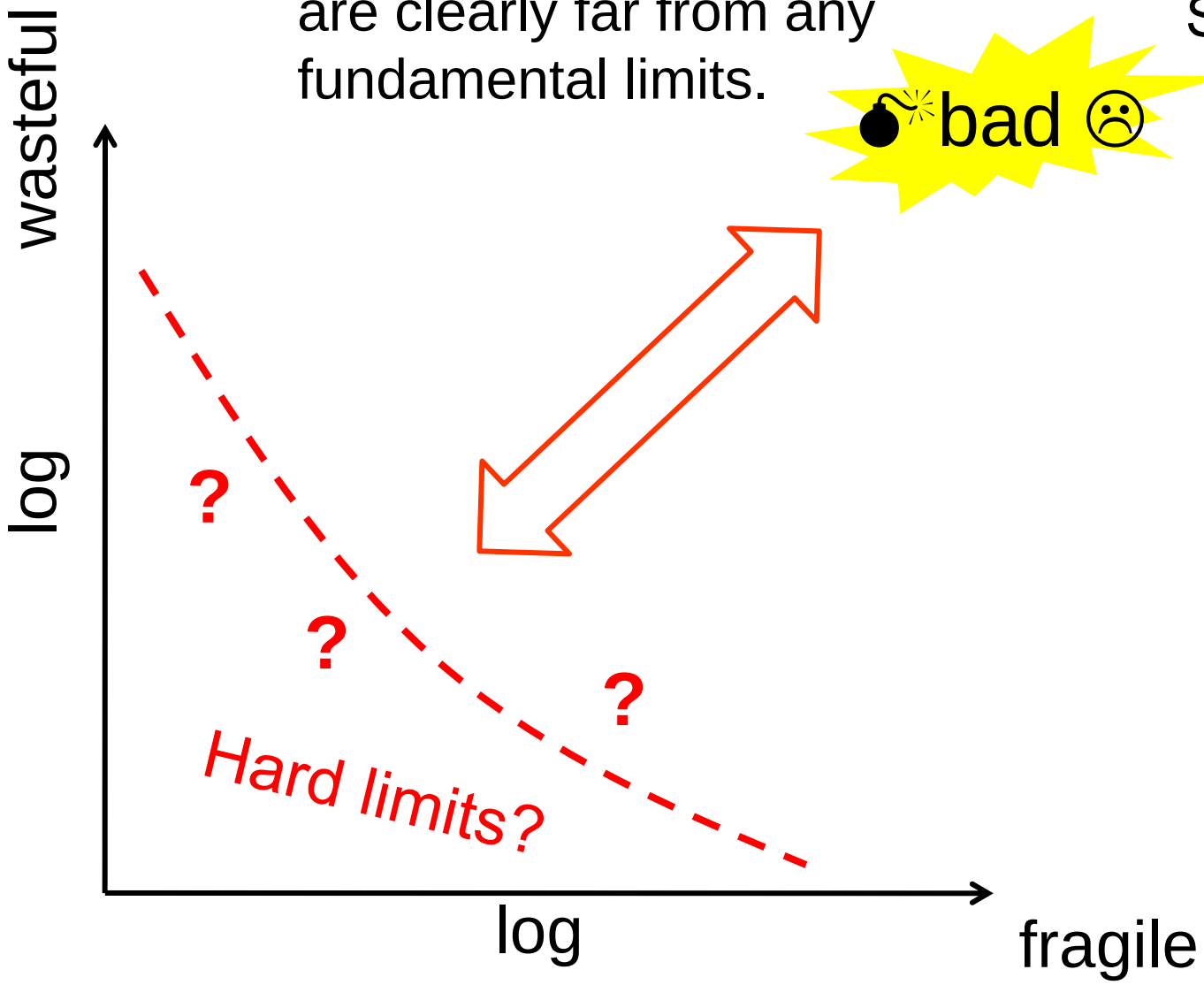
wasteful



But many existing systems and architectures are clearly far from any fundamental limits.

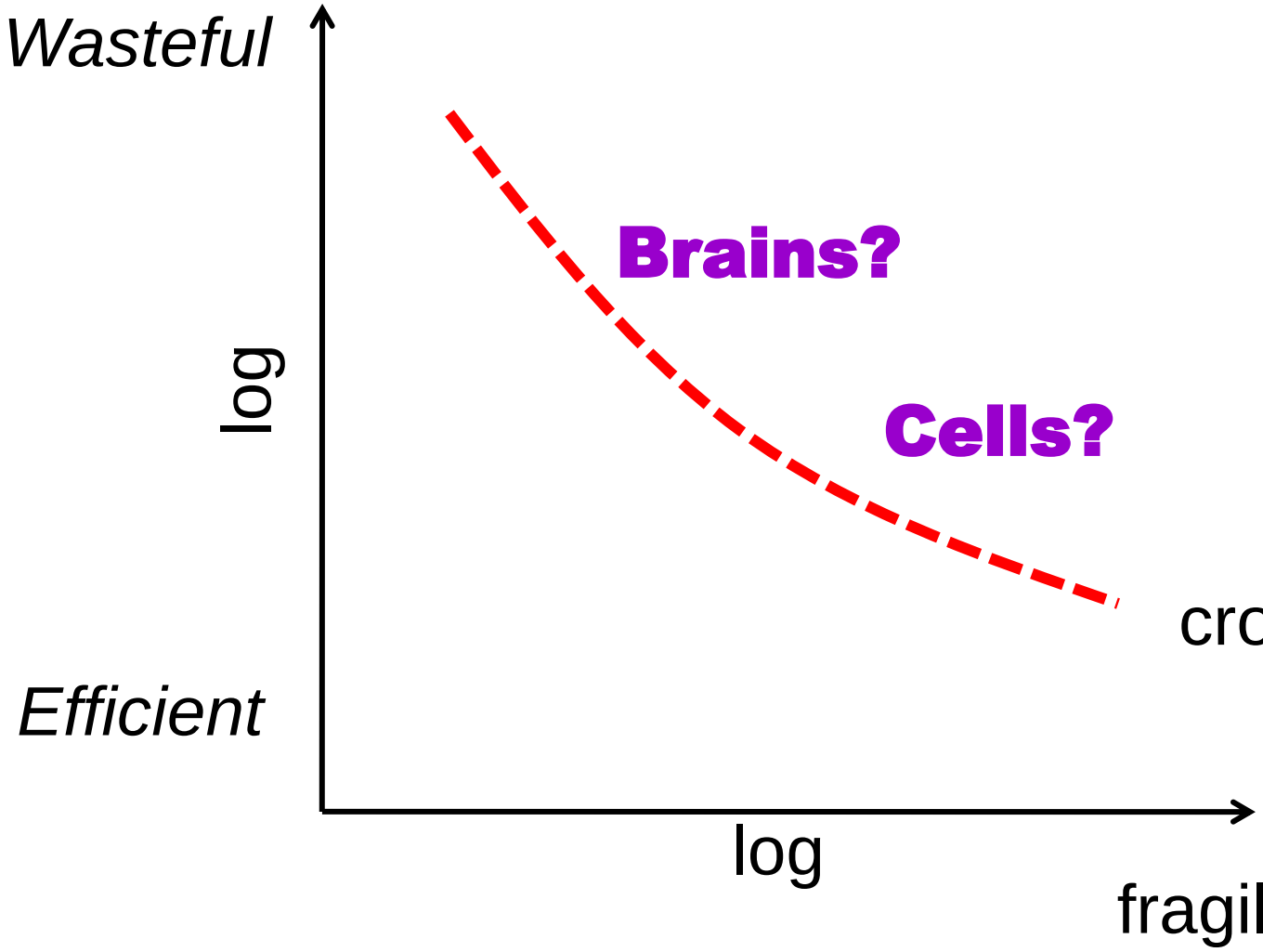
bad ☹

So fixing “bugs” in existing architectures has most immediate impact.



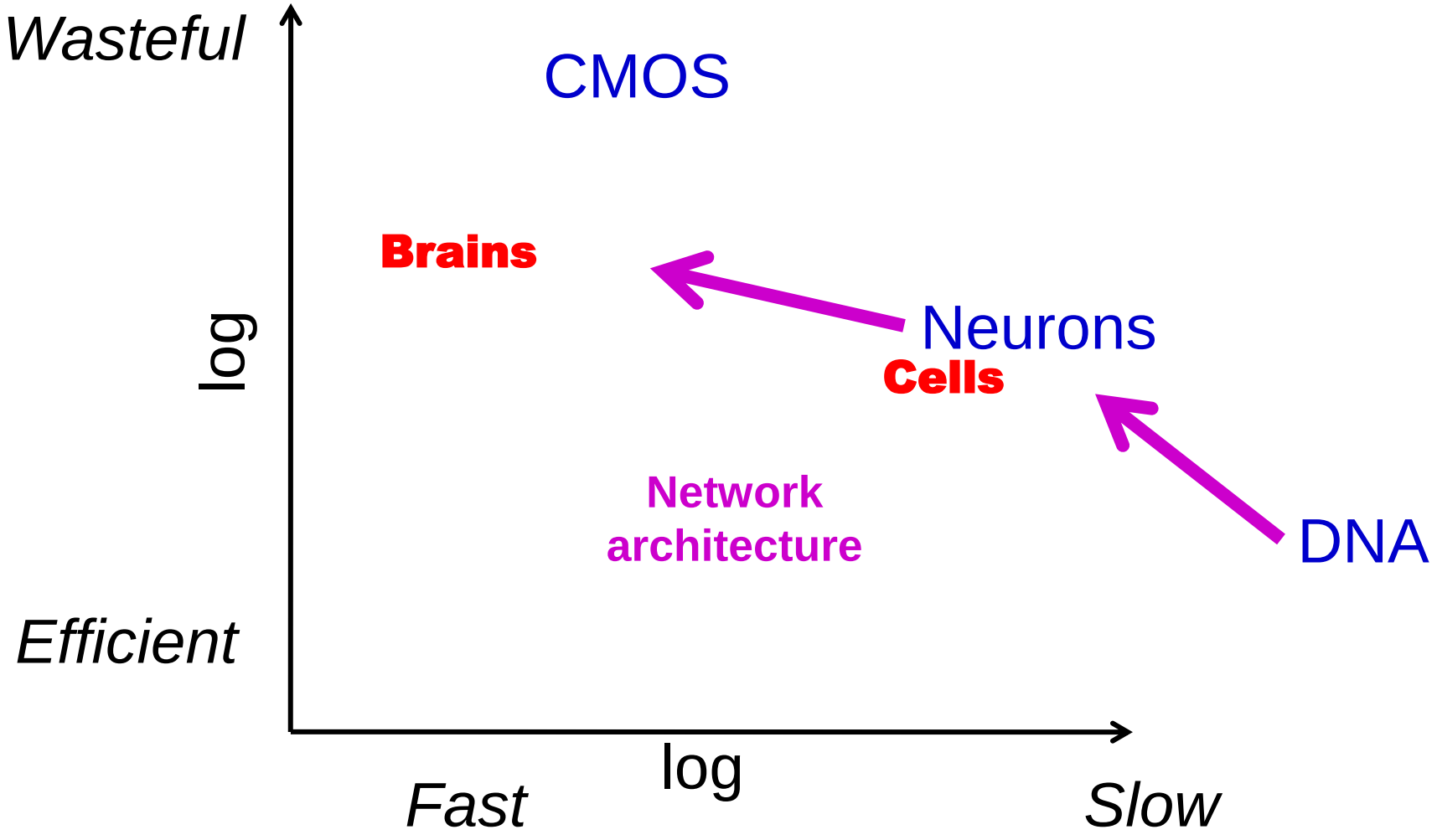
Note: “log” suggests orders of magnitude variations

Conjecture: Cells and brains are RYF but not gratuitously fragile

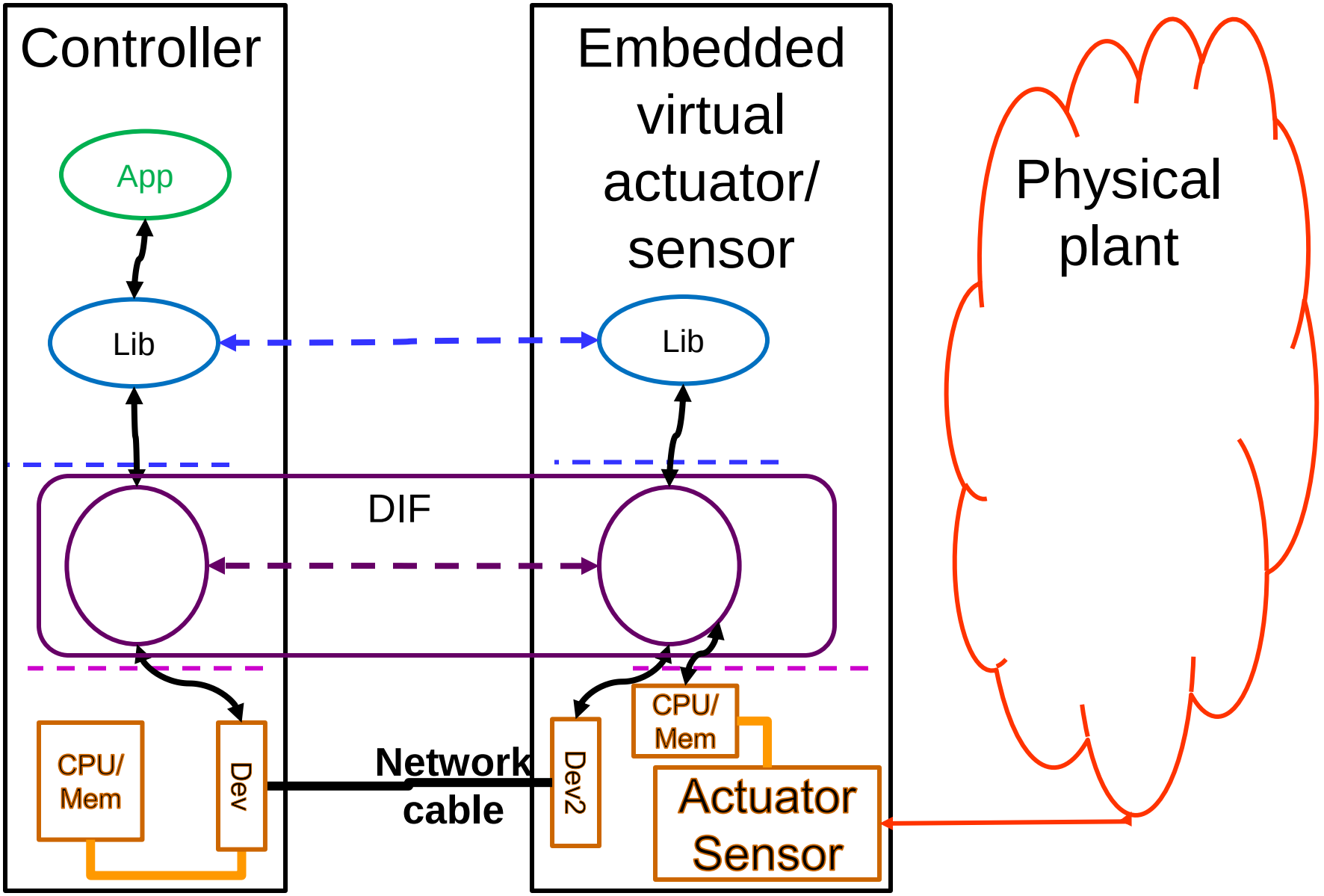


They avoid cross-layering?

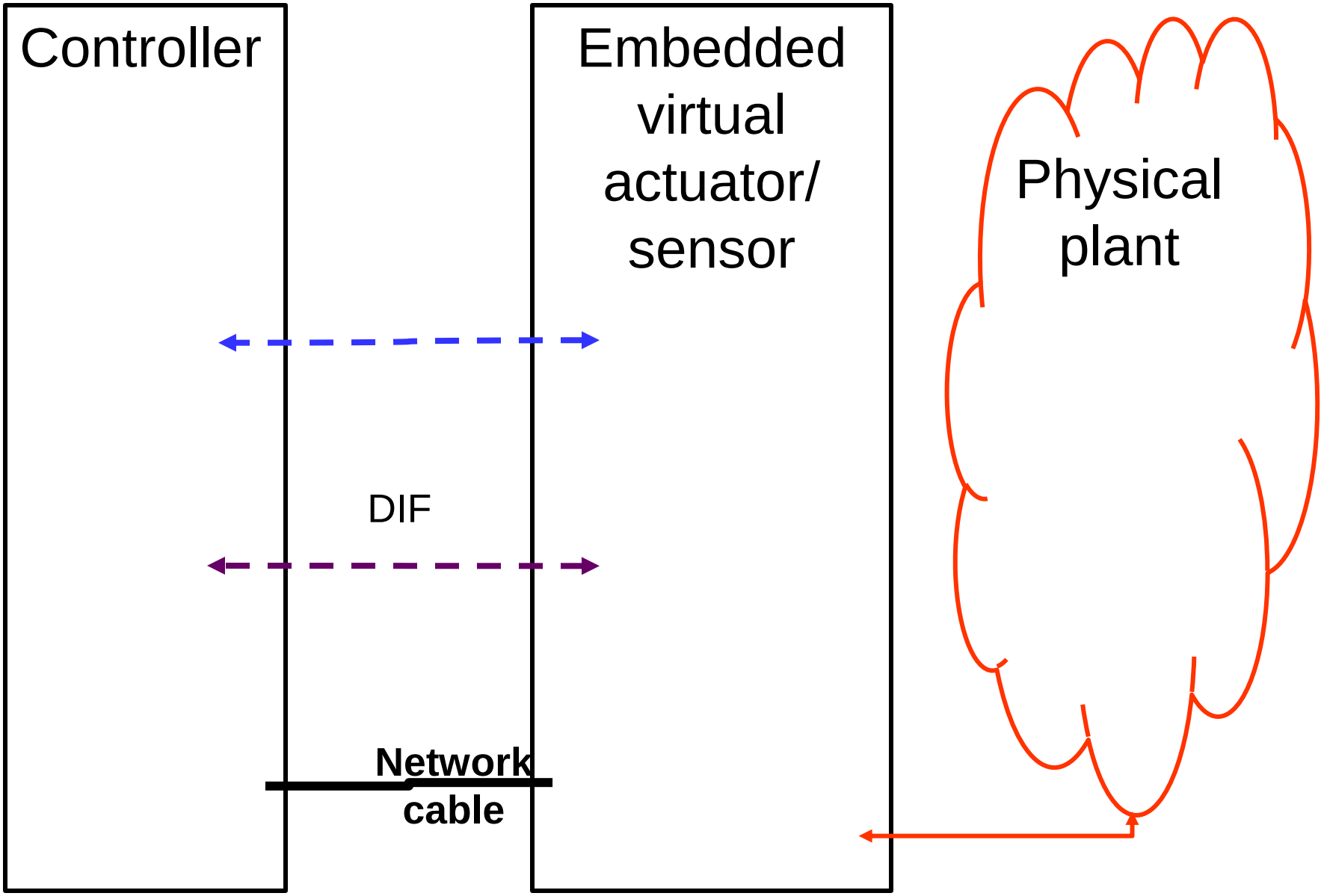
What makes this possible?



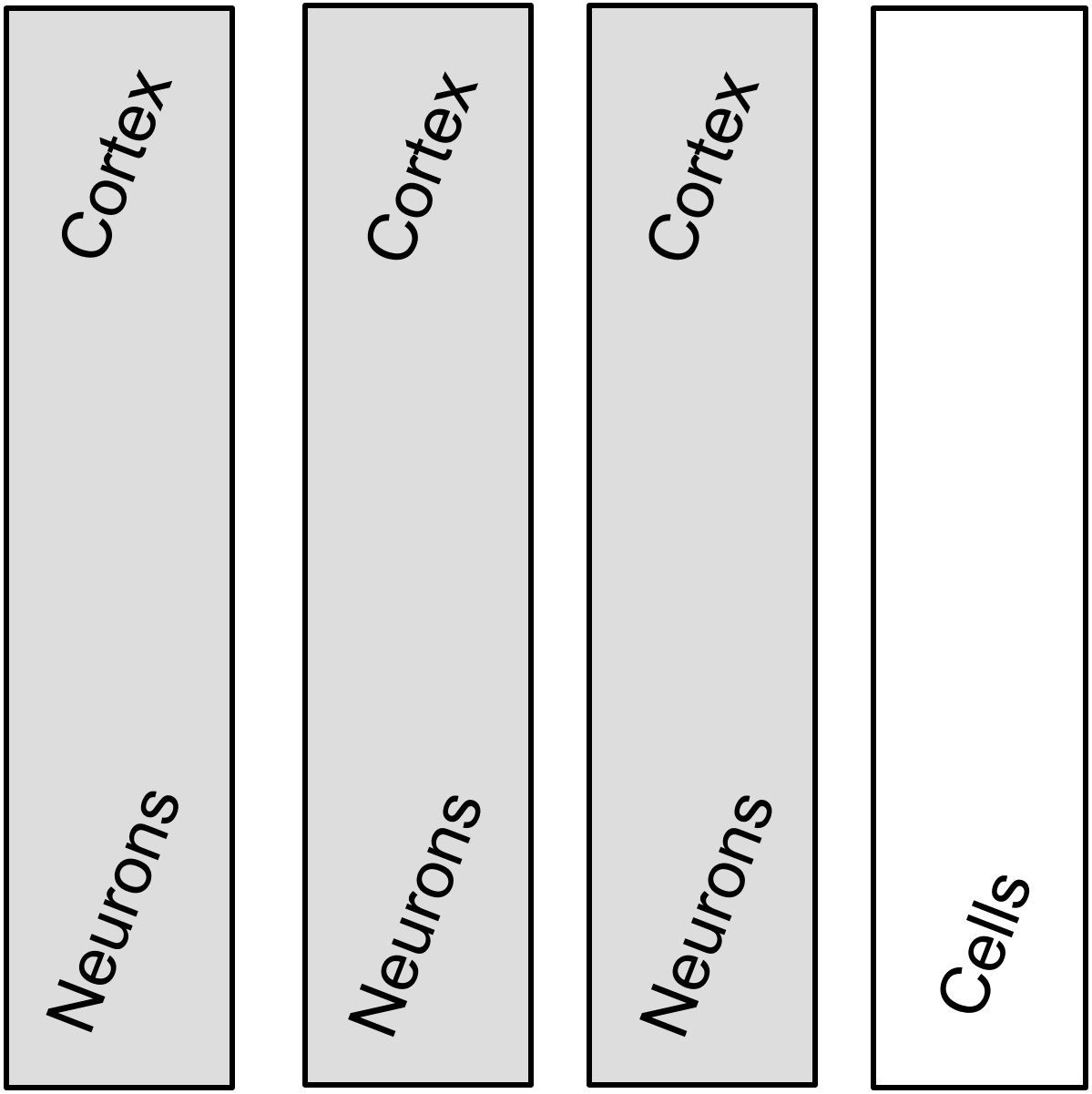
Networked embedded

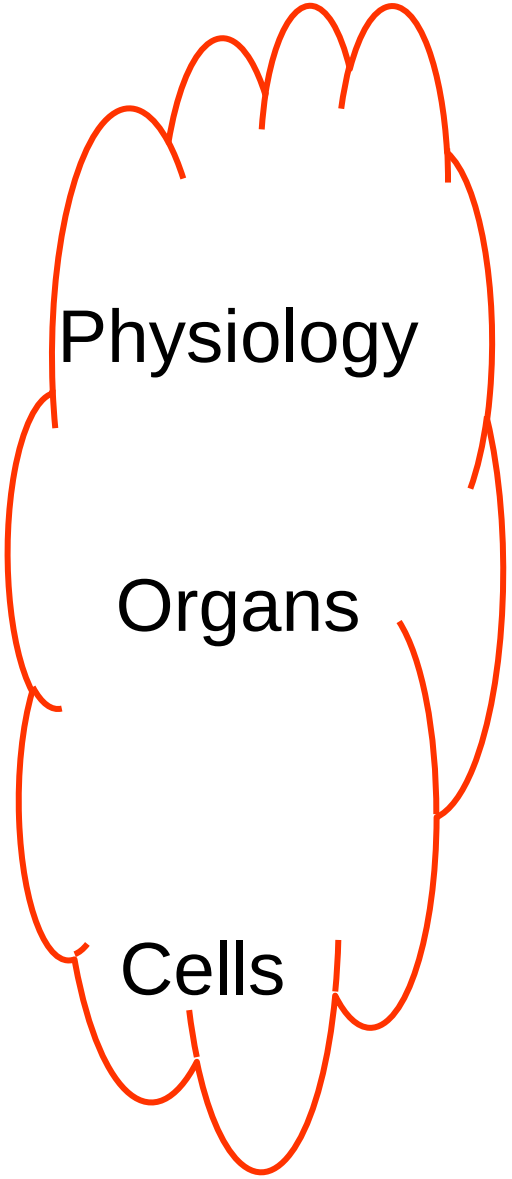


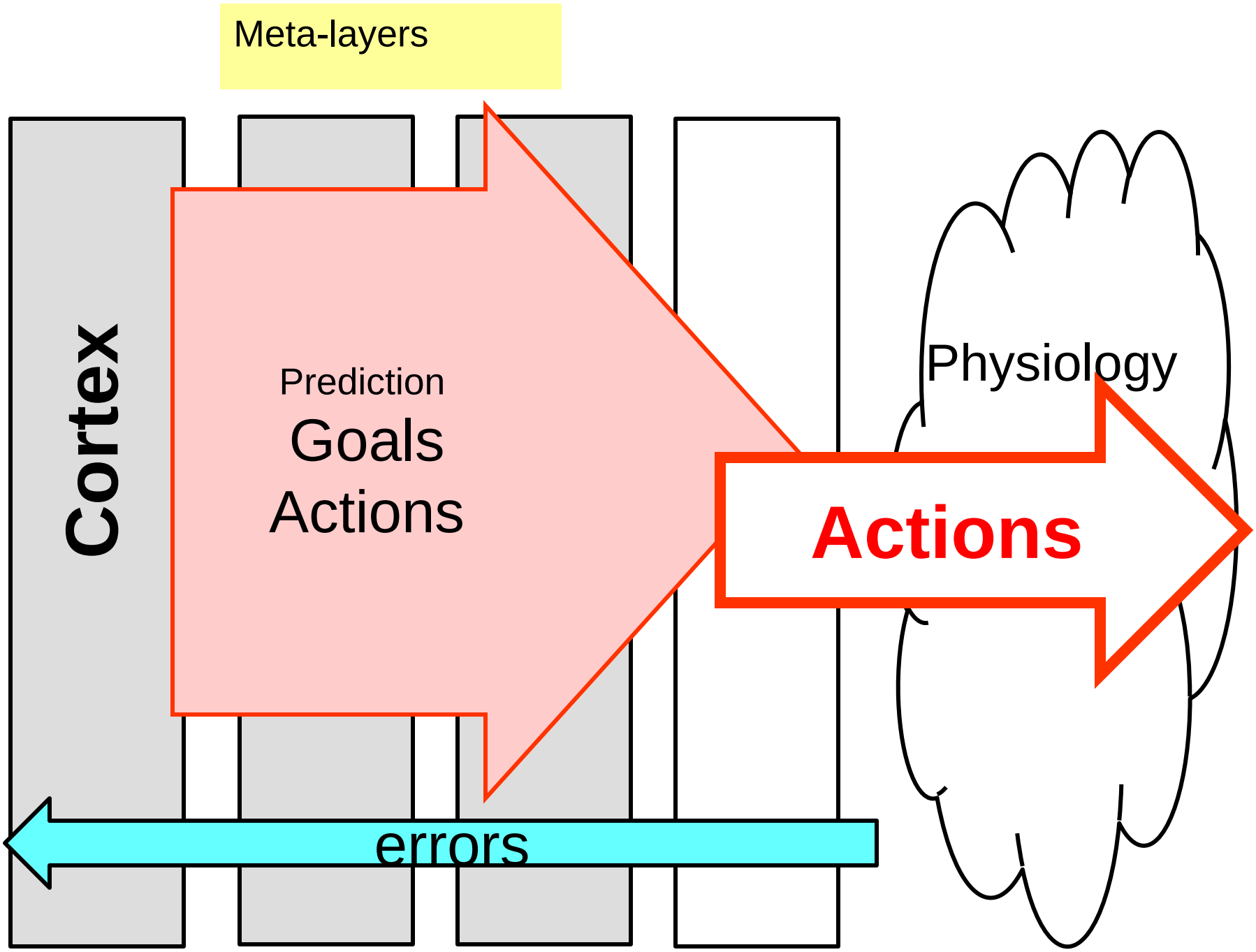
Meta-layering of cyber-phys control

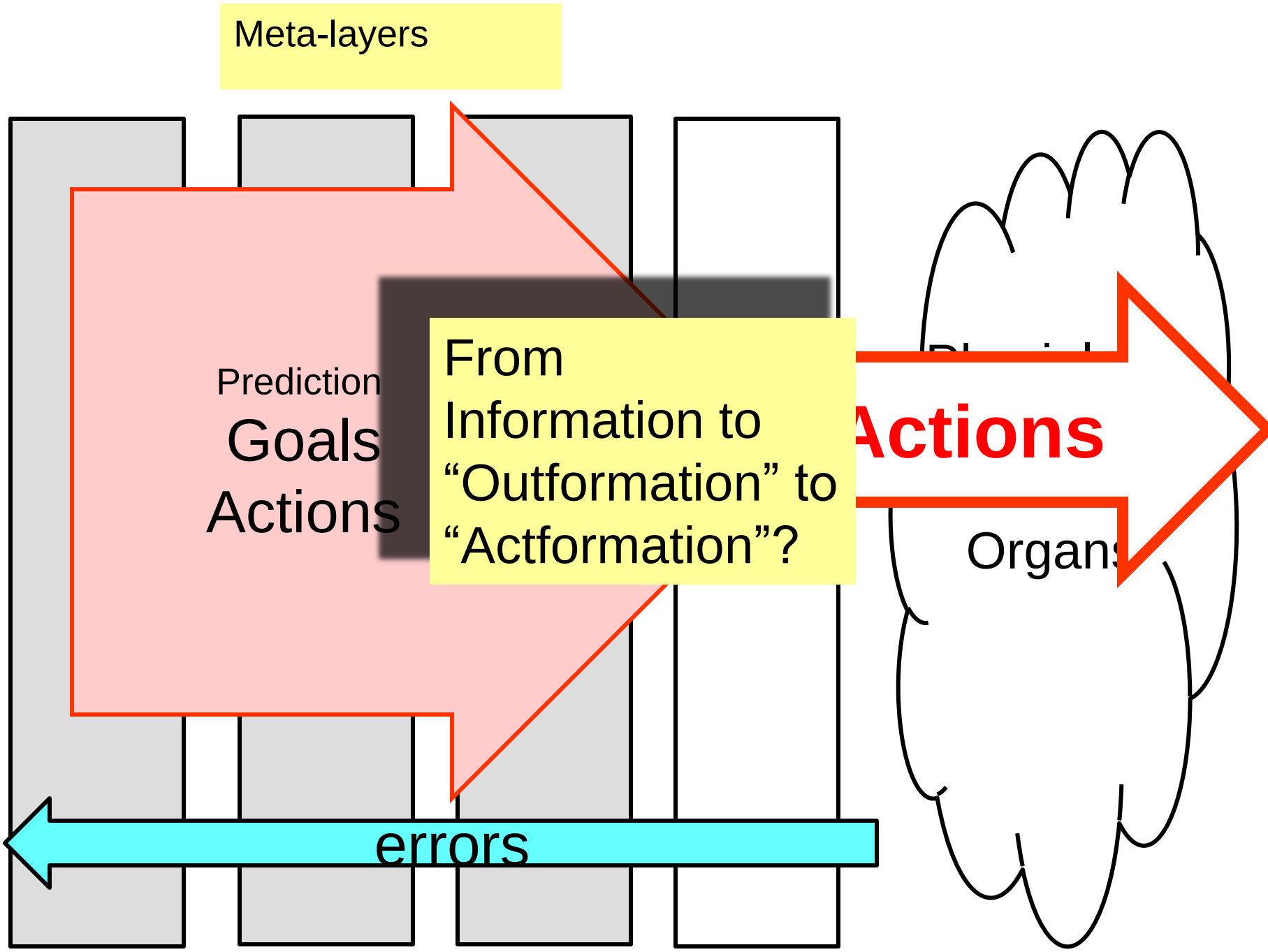


Meta-layers


Cortex
Neurons
Cortex
Neurons
Cortex
Neurons
Cells


Physiology
Organs
Cells


Meta-layers
Cortex
Prediction
Goals
Actions
Physiology
Actions
errors


Meta-layers
Prediction
Goals
Actions
From
Information to
“Outformation” to
“Actformation”?
Actions
Organs
errors

Meta-layers

Cortex

Cortex

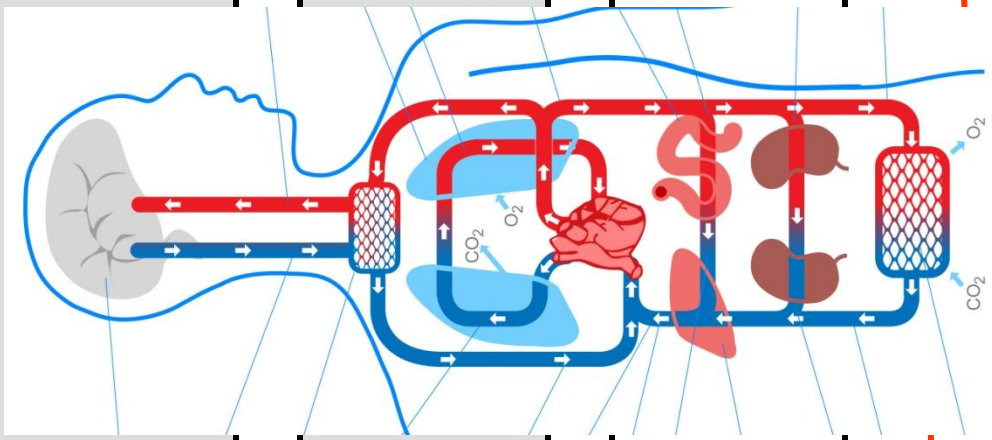
Cortex

Neurons

Neurons

Neurons

Cells



Physiology

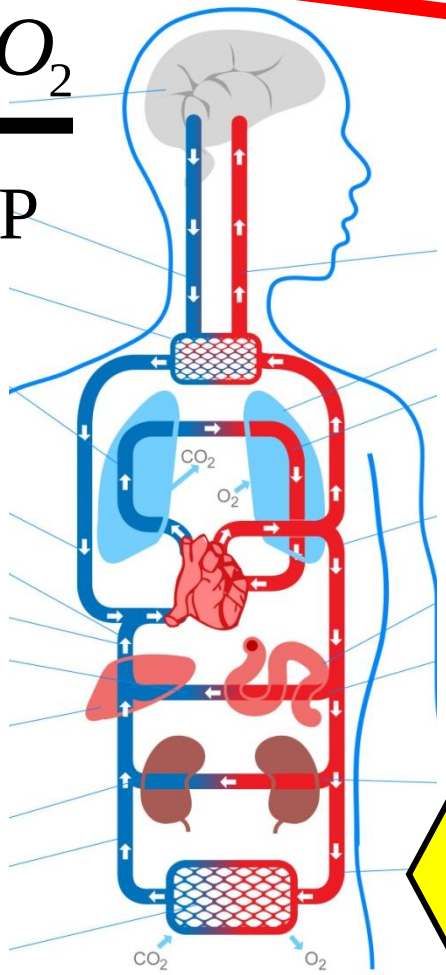
Organs

Cells

Minimize resulting fluctuations in

SpO_2

BP



(Evolution + physiology)

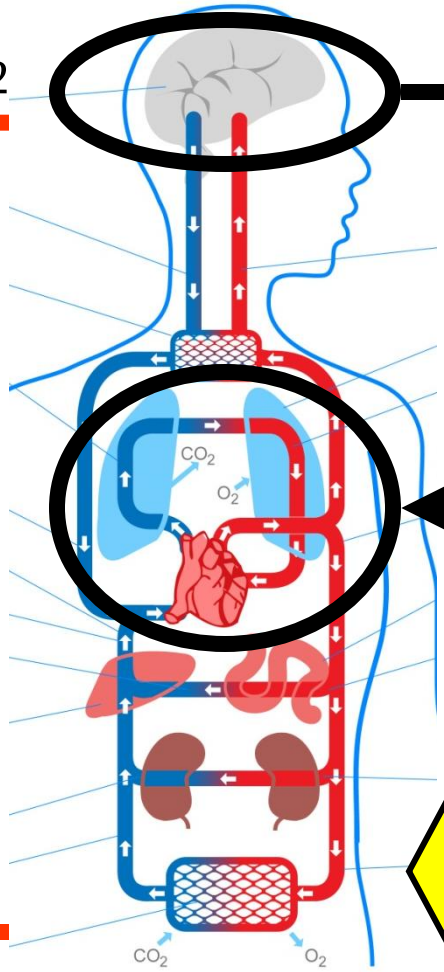
Maximize allowable fluctuations in

watts

Simple starting point.

Control requirement

functional requirements



error

SpO_2

BP

Minimize

error

HR

$\dot{V}_E$

Control

watts

Maximize

Control requirement

Finally VO2 and VCO2 don't need tight control and vary as needed, they don't change as much as watts, but much more than spO2 or BP.